
聲明

本檔案之內容僅供下載人自學或推廣化學教育之非營利目的使用。並請於使用時註明出處。

[如本頁取材自○○○教授演講內容]。



永續化學合成(2)

永續化學的非傳統反應方法與溶劑

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永續化學合成

Plechkova and Seddon said: Your work is not green because you choose to call it green and publish it in *Green Chemistry*. Improving a yield, eliminating a toxic reagent, increasing a selectivity, are all admirable, but just a **green attitude**. **The term green chemistry has to be applied to a total process, not to an single step.** (*Methods and Reagents for Green Chemistry, 2007, p. 110*)

Thus, a better yield or a higher selectivity at a condition not in line with principles of green chemistry or sustainability will not be regarded to have “green attitude,” either.

反應條件、試劑、溶劑、觸媒等都能盡量配合永續化學十二原則與次原則才是永續化學合成 (**sustainable chemical synthesis**)



Non-conventional methods



E-factor is the most important especially from the practical point of view, not only for production, but also for R&D

Alternative activation methods and alternative reaction media are sought for the purpose of **reducing**:

- **Cost**
- **Energy**
- **Environmental impact**
- **Hazards**
- **Materials**
- **Non-renewables**
- **Risk**
- **Waste**

Sustainable chemistry is the **design, manufacture, and use** of environmentally benign **chemical products and processes** to prevent pollution, produce less hazardous waste, and reduce environmental and human risks.

(OECD, 1999)

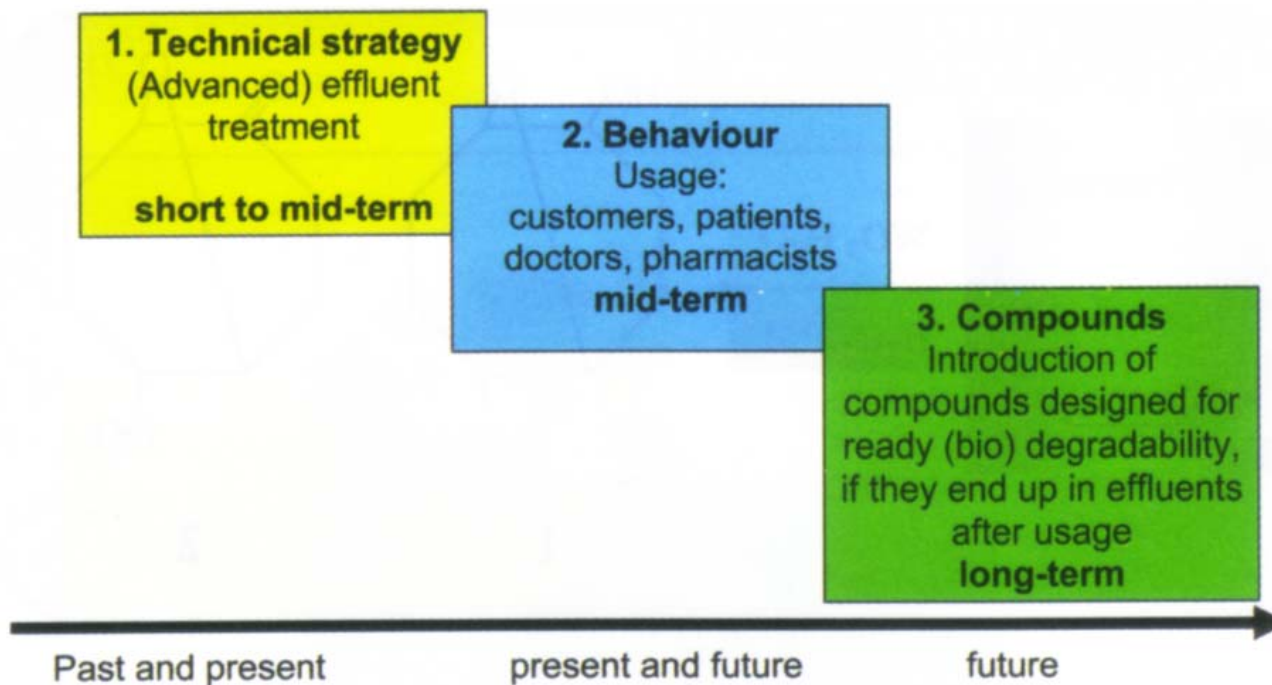


Sustainable from the very beginning

Example: Sustainable from the very beginning: rational design of molecules by life cycle engineering as an important approach for green pharmacy and green chemistry

Klaus Kümmerner *Green Chem.* **2007**, 9(8), 899

Taking into account the full life cycle of chemicals will lead to a different understanding of the full functionality necessary for a chemical. Examples are presented to underline the feasibility and the economic potential of the approach benign by design.





Methods for chemical activation

Energy methods

Thermo chemistry

Photo chemistry

Electro chemistry

Piezo chemistry

Sono chemistry

Microwave chemistry

Mechano chemistry

System requires

Heating

Chromophore, light source

Conducting media

High pressure

Ultrasound source

Polar media, microwave source

Solid, mill-grinding

From sustainability point of view, “greener” technologies with **high energy and material efficiency** are recommended to use.

Examples are **ball milling**, **microwave** irradiation, and **ultrasound** irradiation. (*Green Chem.* 2008, 10, 1129-1130, 1131-1141)



Replacement of volatile organic solvents

Solvent free or minimum solvent used

Solvent alternatives:

Water

Non-Volatile solvents (liquid polymer, fluoruous?)

Solvents from renewable resources (such as ethyl lactate)

Other Benign solvents (ionic liquids, gas-expanded liquids)

Supercritical and near-critical fluid systems

Green solvents for Chemistry: Perspective and Practice, by Nelson, Oxford, **2003**

Green solvents for sustainable organic synthesis (Sheldon, *Green Chem.* **2005**, 7, 267-278.)

Green Reaction Media in Organic Synthesis by Mikami, Blackwell, **2005**

Alternative Solvents: Shades of Green (Clark and Tavener, *Org. Proc. Res. Dev.* **2007**, 11, 149-155)

Solvents from nature (Horváth, *Green Chem.* **2008**, 10, 1024-1028.)

Alternative Solvents for Green Chemistry by Kerton, RSC, **2009**



J. Chu and H. Bienayme (Ed) *Multicomponent Reactions*, Wiley-VCH, 2005

Chemo-differentiating ABB' multicomponent reactions.

D. Tejedor, et al., *Chem. Soc. Rev.* **2007**, 36, 484-491.

Sustainability through green processing—novel process windows intensify micro and milli process technologies

V. Hessel, et al. *Energy Environ. Sci.* 2008, 1, 467-478.

T. Wirth (Ed), *Microreactors in Organic Synthesis and Catalysis*, Wiley-VCH, 2008.

Corning *Advanced-Flow Reactor*, announced May, 2009

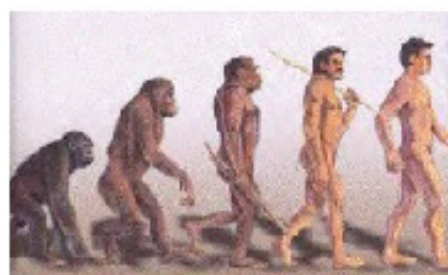
http://www.corning-cable-systems.org/news_center/news_releases/2009/2009040601.aspx

Roesky and Kennepohl (Ed), *Experiments in Green and Sustainable Chemistry*, Wiley-VCH, 2009.

R. Ballini (Ed), *Eco-Friendly Synthesis of Fine Chemicals*, RSC, 2009



Evolution (Revolution) in Chemical Processing



Glass Fluidic Modules



Corning® Advanced-Flow™ Glass Reactor



Alchemy



Today's Industrial Manufacturing



CORNING

© Corning Incorporated 2009

**Georgia Tech to Use Corning Advanced-Flow Reactor
in Chemical Synthesis Research since April, 2010**



Solvent-free Reactions



Reduction	Rearrangement
Oxidation	Elimination
C-C Bond formation	Protection (bond formation)
C-N Bond formation	De-protection (bond-breaking)
C-O Bond formation	Complex formation
C-S Bond formation	Salt formation
C-P Bond formation	Guest-host reaction
C-Halogen Bond formation	Isomerization
N-N Bond formation	Polymerization, etc.

(K. Tanaka, *Solvent-free Organic Synthesis*, Wiley-VCH, 2003.)

F. Toda (Ed), *Top. Curr. Chem. 2005, Vol. 254* (Organic Solid State Reactions)

Z. V. Todres, *Organic Mechanochemistry and its Practical Applications*, CRC/Taylor & Francis, 2006.

P. J. Walsh, *et al. Chem. Rev. 2007, 107, 2503-2545*. (solvent-free and highly concentrated reactions)

Chem. Soc. Rev. 2007, 36, 846-855 (metal complexes), *1239-1248* (metal ion catalyzed reactions).

Chapter 2 in *Alternative Solvents for Green Chemistry* RCS, 2009

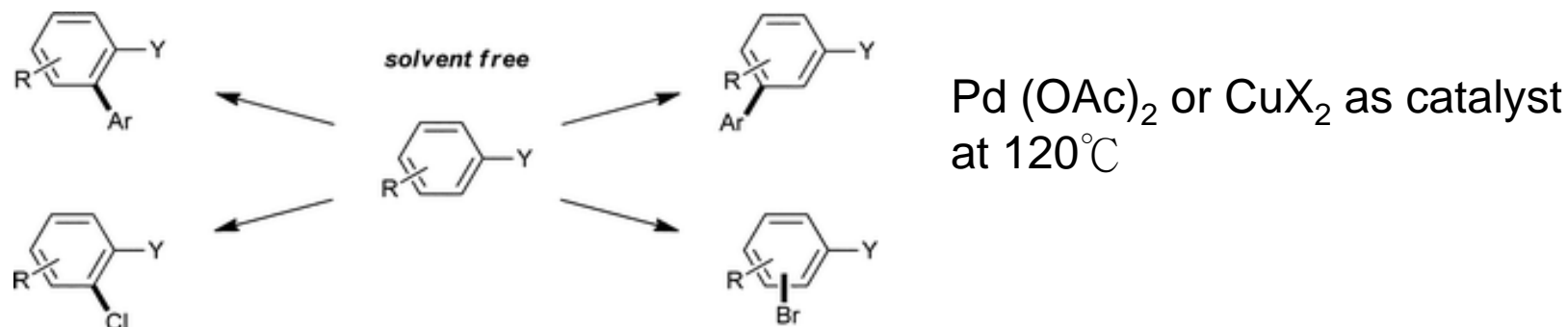


Solvent-free Reactions

Solvent free catalytic C–H functionalisation

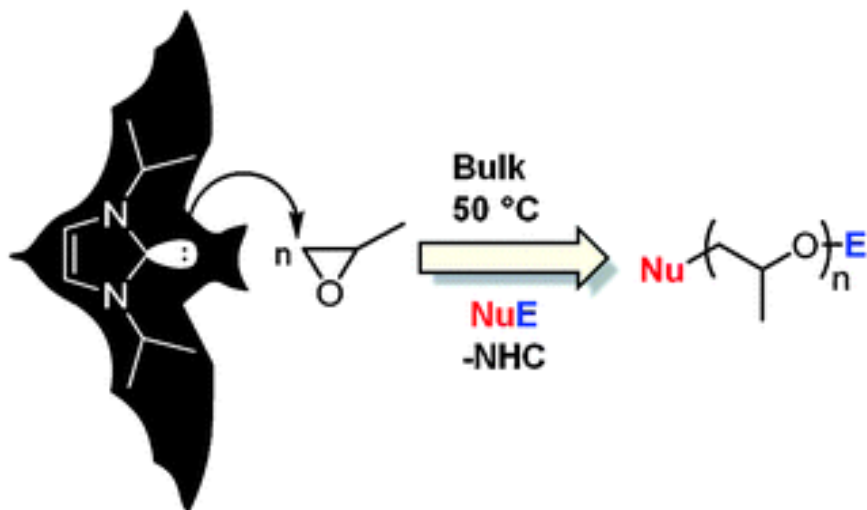
(Bedford, *et al. Chem. Commun.*, 2010, 46, 3095 - 3097,)

Arylation or halogenation of aryl carbamates and anilides (40-90% yield)



N-heterocyclic carbene-induced ring opening polymerization

(Raynaud, *et al. Chem. Commun.*, 2010, 46, 3203 - 3205)



Metal-free and solvent-free
30-40% conversion to oligomers in
3 days



Advantages of using solvent-free conditions

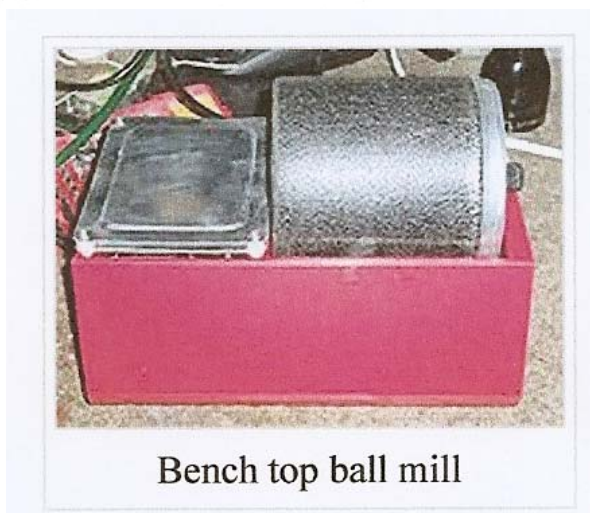
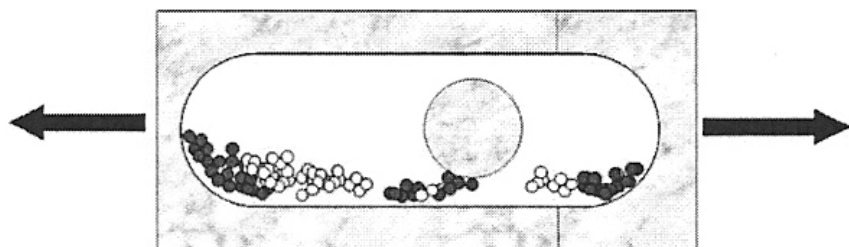
1. There is no reaction media to collect, dispose of, or purify and recycle.
2. On a laboratory's preparative scale, there is often no need for specialized equipment.
3. Extensive and expensive purification procedures such as chromatography can often be avoided due to the formation of sufficiently pure compounds.
4. Greater selectivity is often observed.
5. Reaction times can be rapid, often with increased yields and lower energy usage.
6. Economic considerations are more advantageous, since cost savings can be associated with the lack of solvents requiring disposal or recycling.
7. **Can be applied to solid-solid, solid-liquid, solid-gas, liquid-liquid, and liquid-gas reactions**



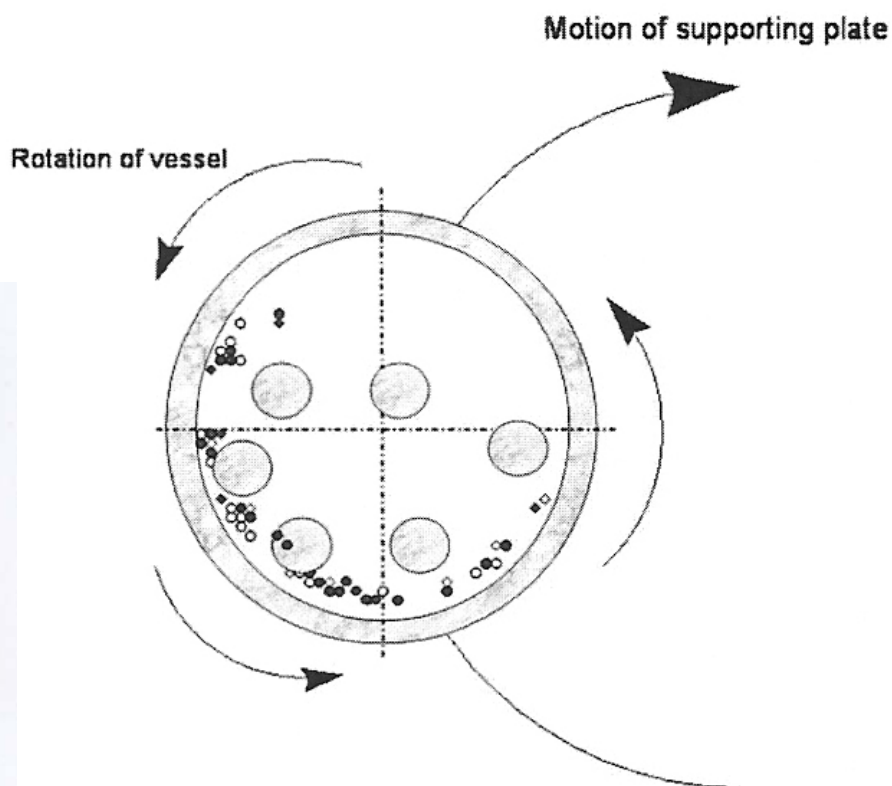
Commercial ball mills

For a solid-state reaction to take place, the reactants have to be vigorously mixed by applying external mechanical energy, and may be called **mechanochemistry**.

- a shaker mill (vibration)



- a planetary mill (rotation)





High speed vibration mill (HSVM)

HSVM at the speed of 3500 rpm was developed by Komatsu and coworkers. A pressure of 10-20000 bar may be generated.

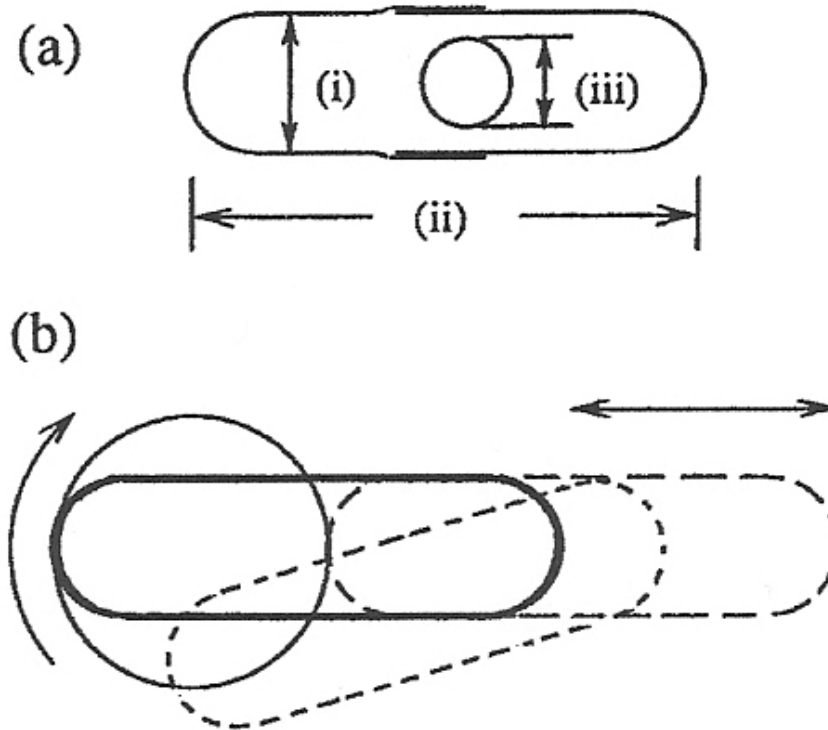
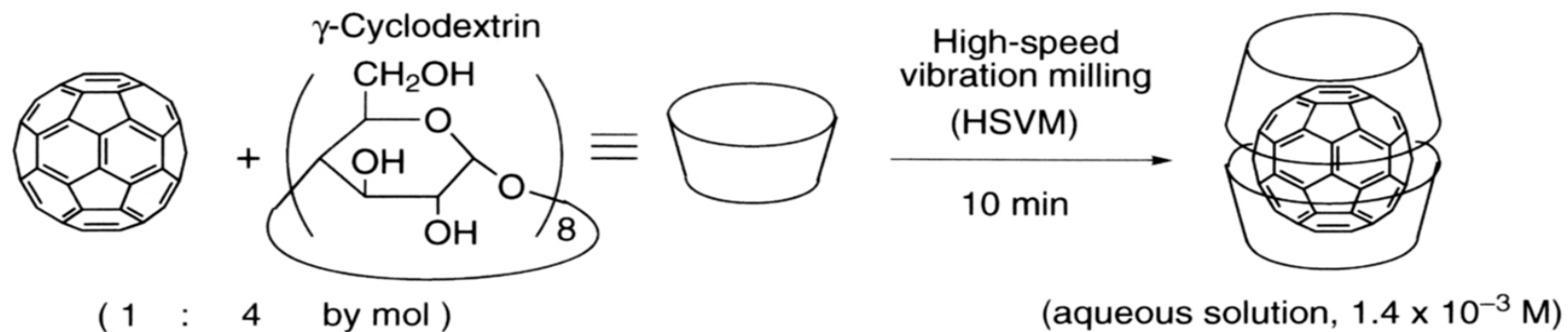


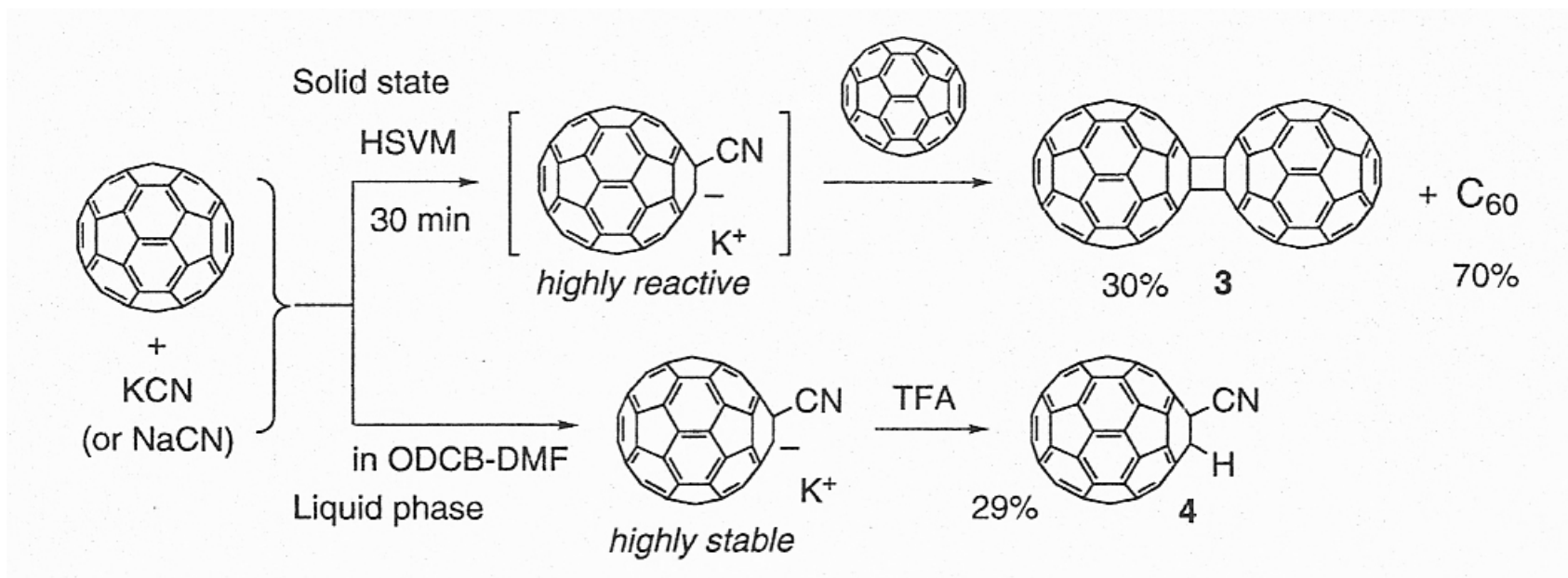
Figure 13. (a) A mixing capsule with a milling ball: (i) inner diameter, 9.0 mm; (ii) inner length, 26 mm; (iii) diameter, 6.0 mm. (b) Schematic representation of the movement of the capsule: one end moves around a circle while the other end moves horizontally.



Guest-Host interaction

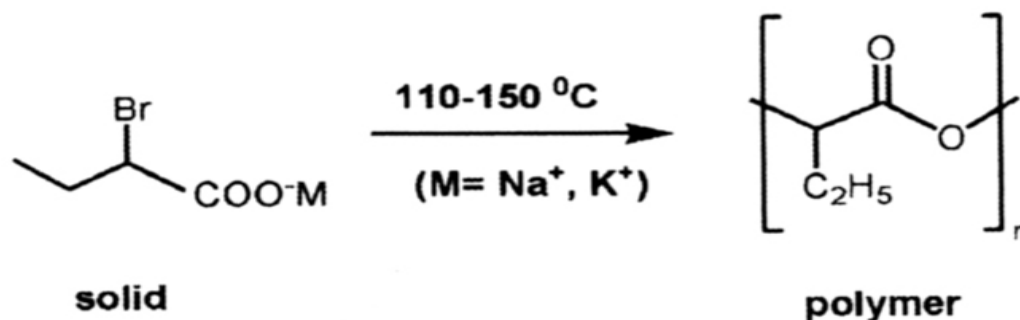


Dimerization of C-60

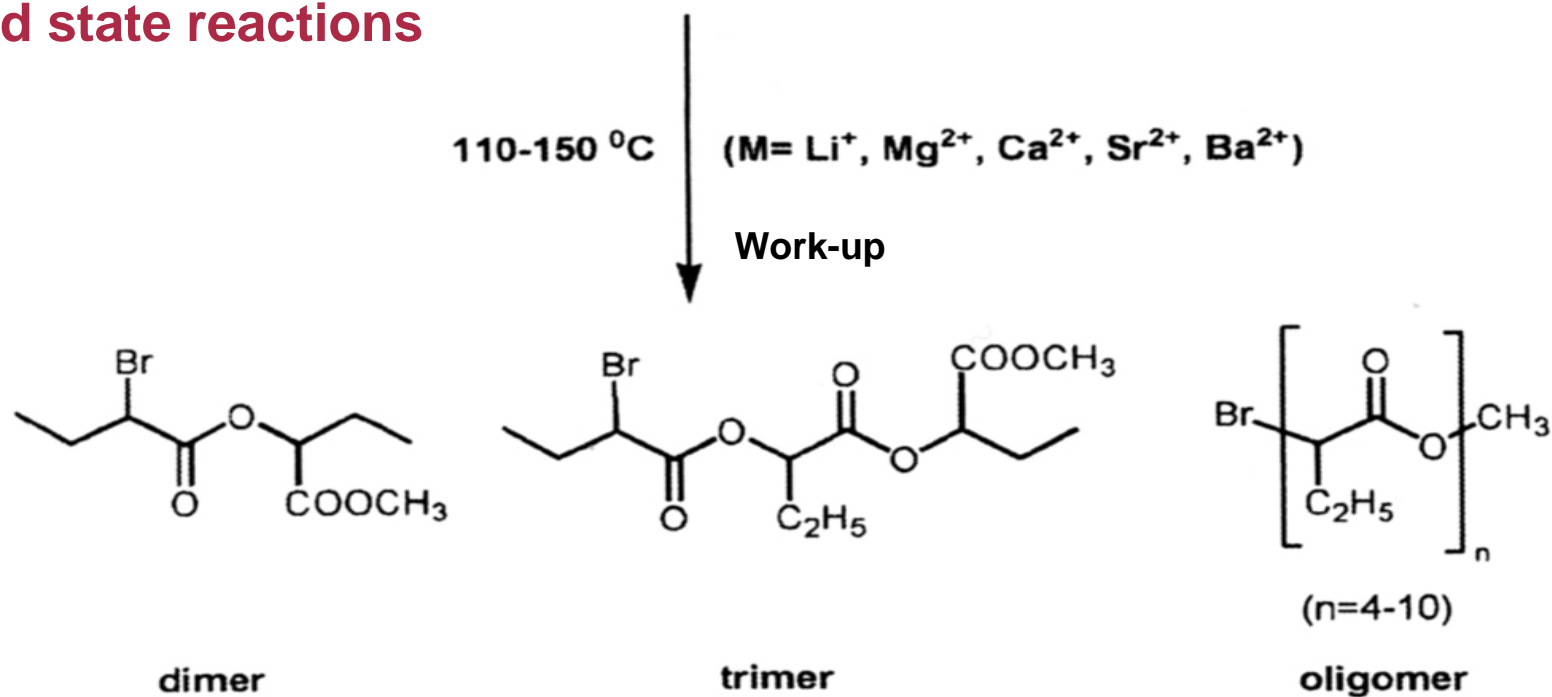




Mechanically induced polymerization



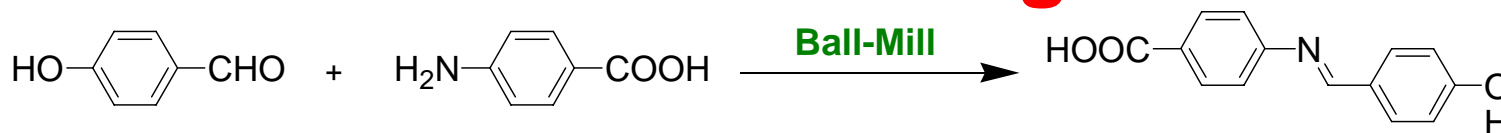
Solid state reactions





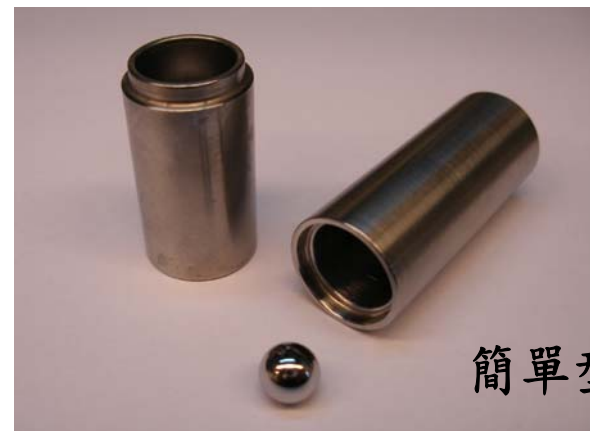
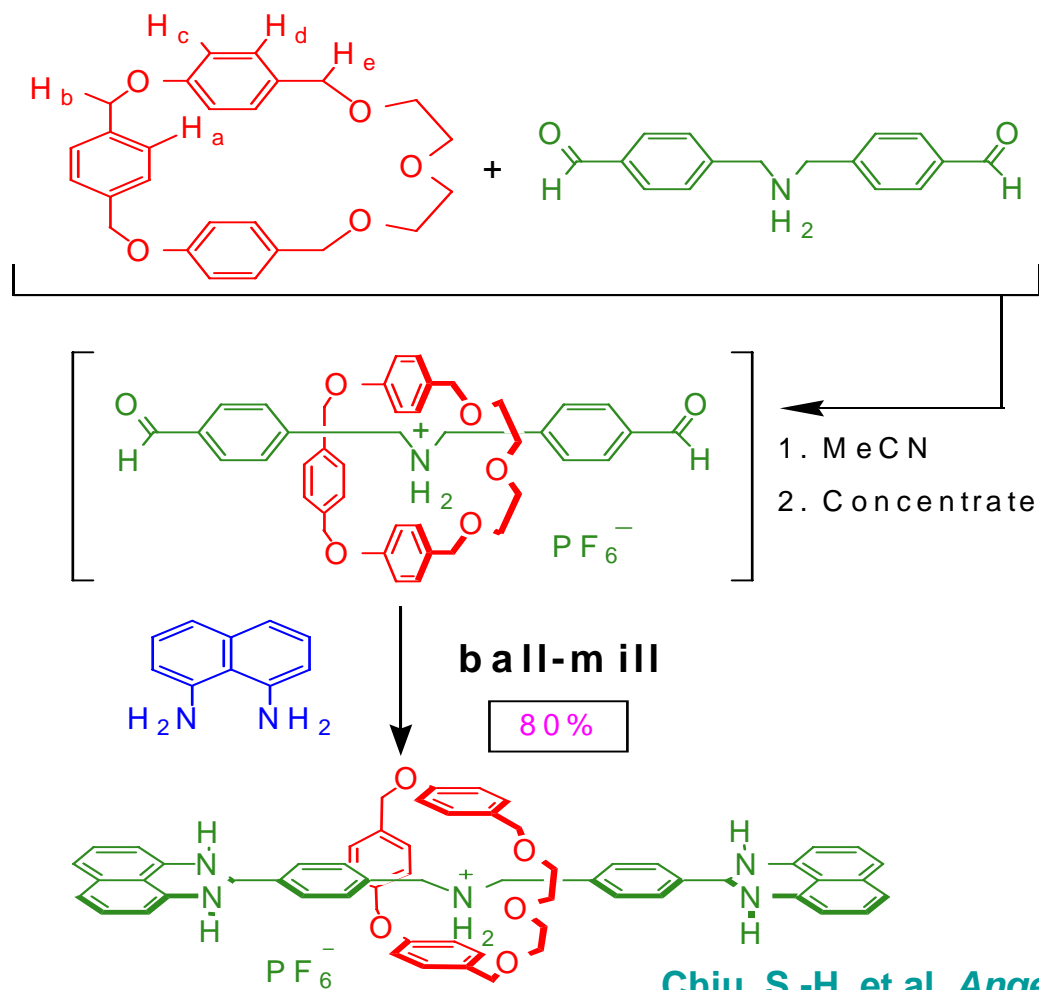
Solid-to-Solid Ball-Milling Process

Imine



Kaupp, et al. *Chem. Engin. Sci.* 2002, 57, 763

[2]-Rotaxane

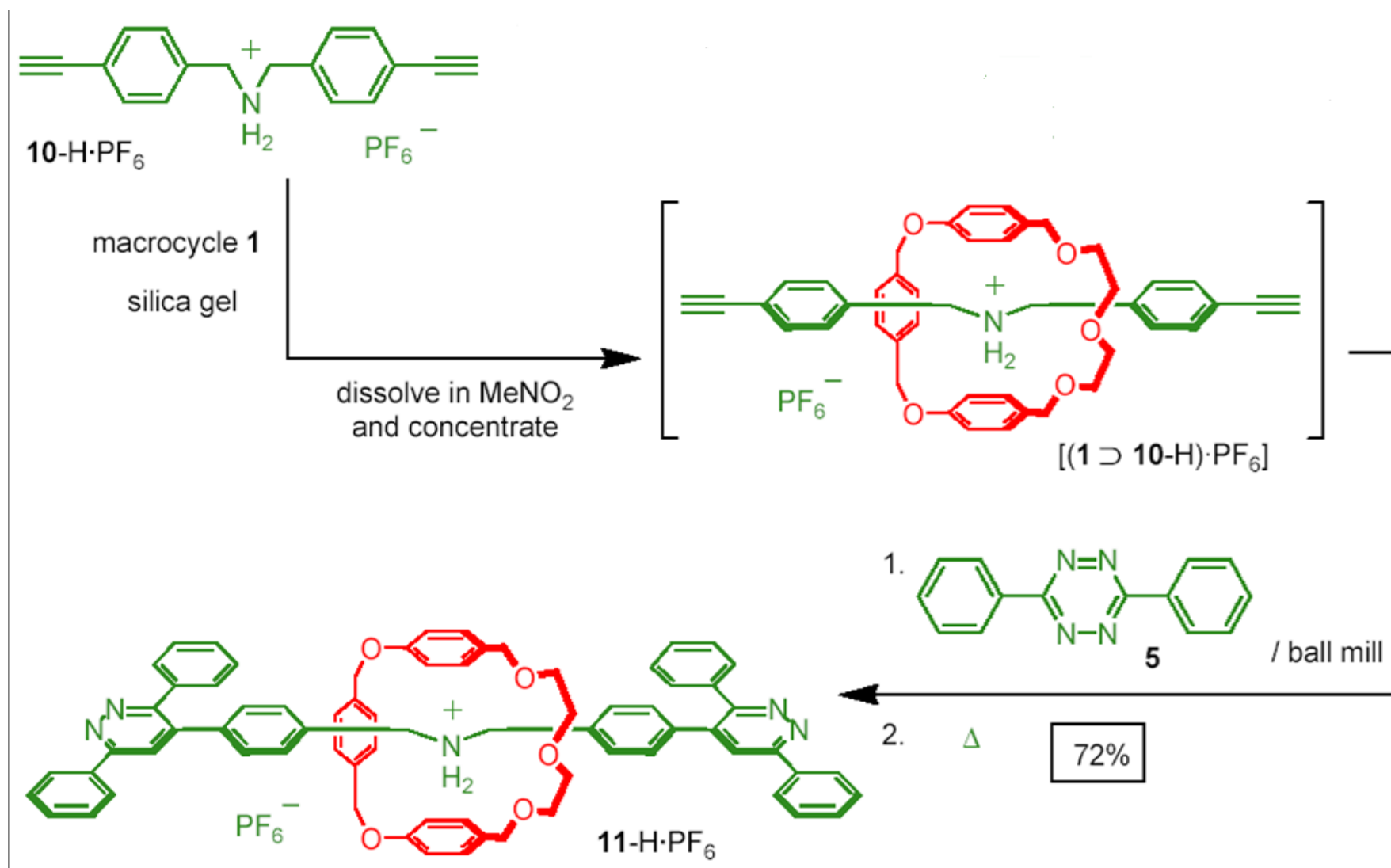


簡單型儀器



16

Chiu, S.-H. et al. *Angew. Chem. Int. Ed.* 2008, 47, 4436-4439



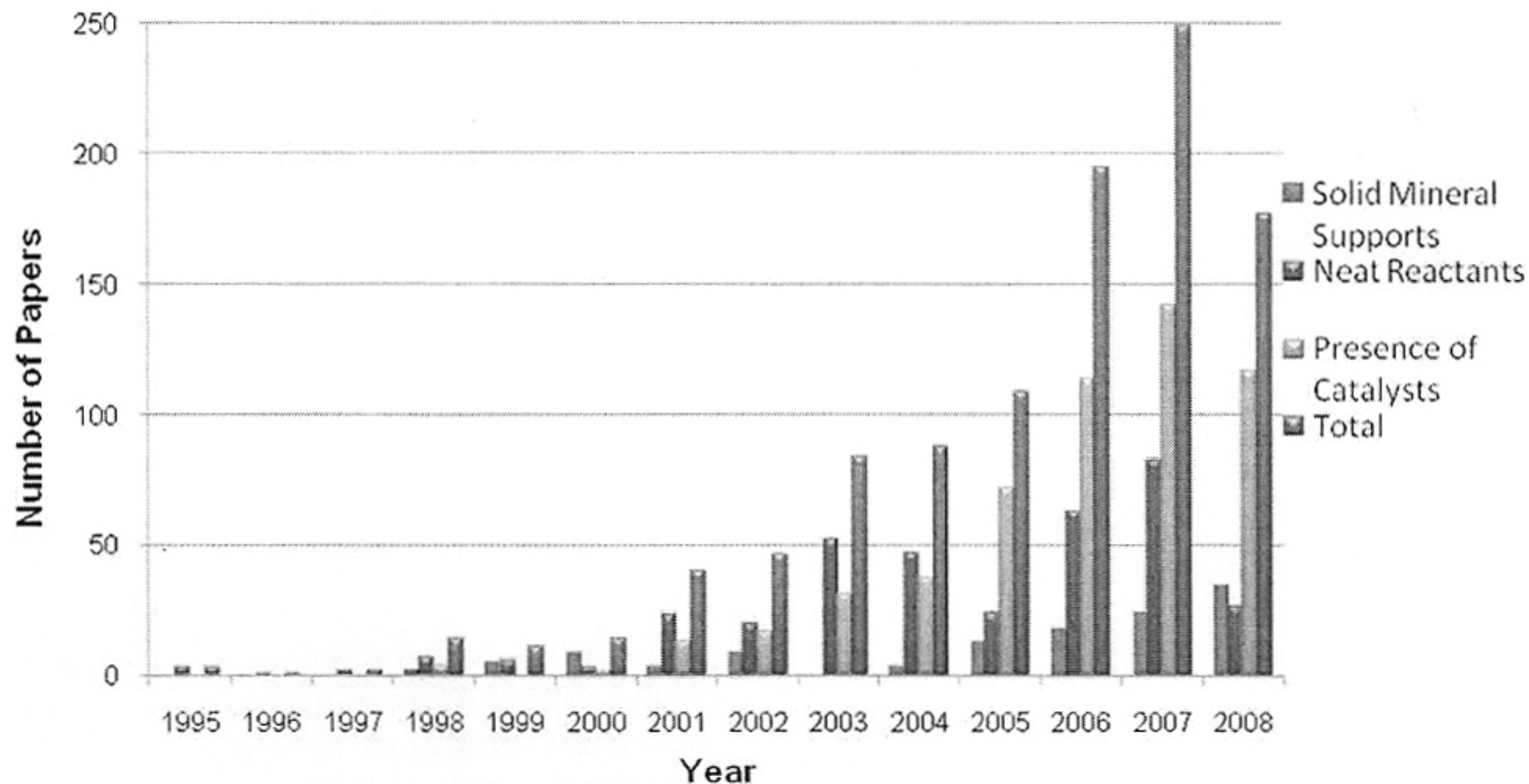


Solvent-free Heterocyclic Synthesis



M. A. Martins, et al., *Chem. Rev.* **2009**, *109*, 4140-4182

Distribution of papers dealing with synthesis of heterocyclic compounds under solvent-free condition by year



Heating, microwave irradiation, ultrasound irradiation, and grinding



The Use of Microwave Irradiation

COST Chemistry Action D32, starting in 2004

(Co-opération Européenne dans le Recherche Scientifique et Technique, European Co-operation in the Field of Scientific and Technical Research)

Four microwave-based working groups involving collaboration between scientists with different expertise in modern technology:

1. Diversity oriented synthesis under **high efficient microwave conditions**. The objectives are:
 - (a) to apply **solvent-less** condition and **alternative reagents** to known reactions;
 - (b) to perform organic reactions in **aqueous media**;
 - (c) to evaluate multi-component reactions under **microwave and/or micro-reactor** condition to minimize waste and optimize atom-efficiency in comparison with conventional stepwise reaction under traditional conditions;
 - (d) to establish, in a combinatorial approach, novel atom economic **multi-component reactions assisted by microwave and/or micro-reactor** technology to efficiently access pharmaceutical applications.



2. **Microwave** and high-intensity **ultrasound** in the synthesis of fine chemicals.
3. **Ultrasound and microwave-assisted** synthesis of nanometric particles.
4. Development and design of **reactors** for microwave-assisted chemistry in the laboratory and on the pilot scale.

The objective of COST D32 is to establish a firm EU base in microwave chemistry and to exploit the new opportunities provided by microwave techniques singly or in appropriate combination, for the widest range of applications in modern chemistry.

References:

- A. Loupy (Ed), *Microwaves in Organic Synthesis, 2nd Edition, 2 Vols*, Wiley-VCH, 2006
- C. O. Kappe and A. Stadler, *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, 2005
- Microwave dielectric heating in synthetic organic chemistry*, C. O. Kappe, *Chem. Soc. Rev.* 2008, 37, 1127-1139
- C. O. Kappe, *et al.*, *Practical Microwave Synthesis for Organic Chemists*, Wiley-VCH, 2009



Characteristics of microwaves

electromagnetic waves with low energy photon

Microwave-matter interaction

causes movement of molecules (dipolar rotation)

causes movement of ions (ionic conduction)

will be reflected, transmitted or absorbed

volumetric heating throughout an absorbing material

Microwave effects

thermal effects – dipolar polarization

superheating in a mw cavity

non-thermal effects – increasing pre-exponential factor A

decreasing activation energy

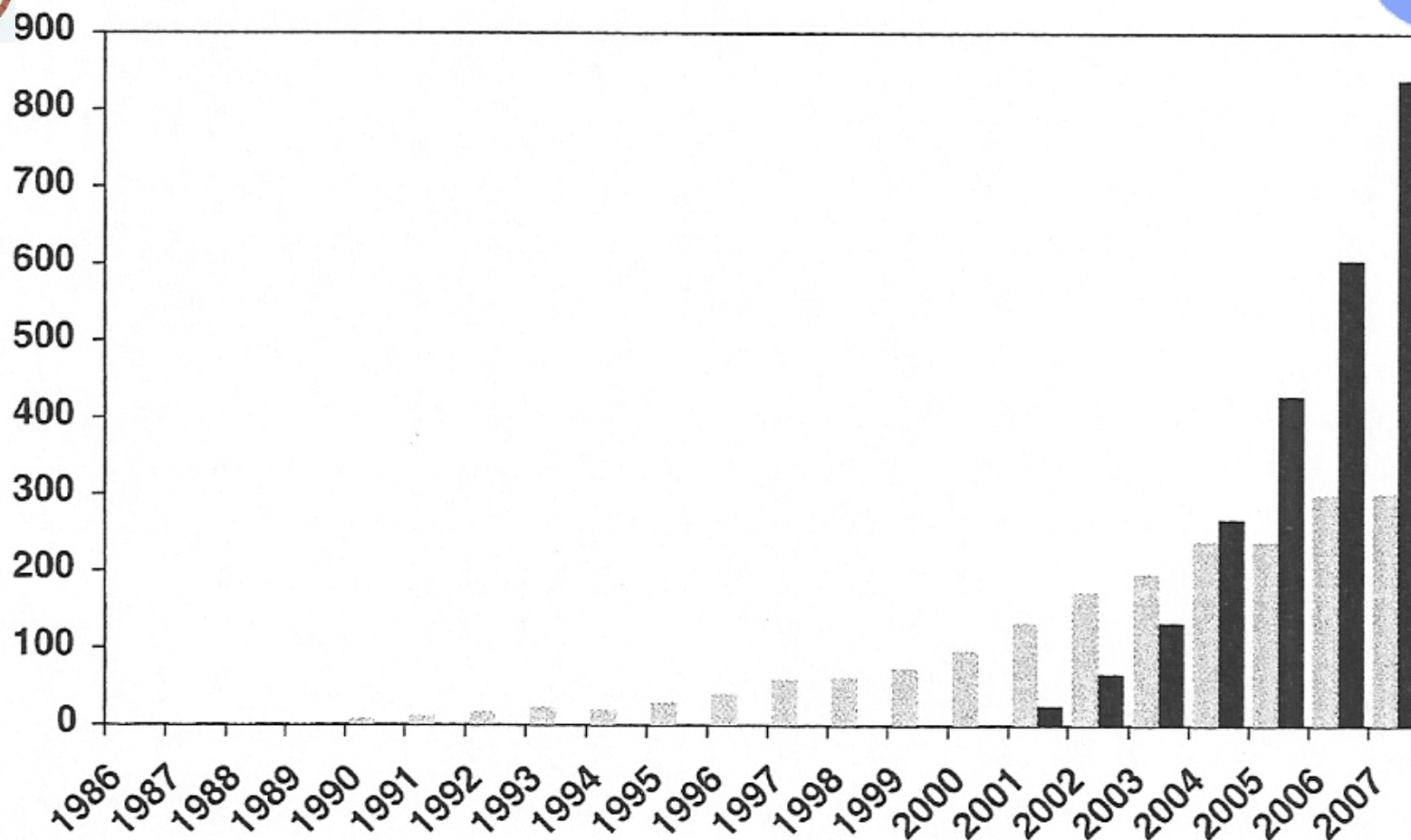


Figure 1.1 Publications on microwave-assisted organic synthesis (1986–2007). Gray bars: Number of articles involving MAOS for seven selected synthetic organic chemistry journals (*J. Org. Chem.*, *Org. Lett.*, *Tetrahedron*, *Tetrahedron Lett.*, *Synth. Commun.*, *Synthesis*, *Synlett*). SciFinder Scholar keyword search on

“microwave”). The black bars represent the number of publications (2001–2007) reporting MAOS experiments in dedicated reactors with adequate process control (about 50 journals, full text search: microwave). Only those articles dealing with synthetic organic chemistry were selected. (Kappe, 2009, p. 4)



Loss tangents ($\tan \delta$ of solvents at 2.45 GHz and 20°C)

Solvent	$\tan \delta$	Solvent	$\tan \delta$
Ethylene glycol	1.350	N,N-dimethylformamide	0.161
Ethanol	0.941	1,2-dichloroethane	0.127
Dimethyl sulfoxide	0.825	Water	0.123
2-propanol	0.799	Chlorobenzene	0.101
Formic acid	0.722	Chloroform	0.091
Methanol	0.659	Acetonitrile	0.062
Nitrobenzene	0.589	Ethyl acetate	0.059
1-butanol	0.571	Acetone	0.054
2-butanol	0.447	Tetrahydrofuran	0.047
1,2-dichlorobenzene	0.280	Dichloromethane	0.042
1-methyl-2-pyrrolidone (NMP)	0.275	Toluene	0.040
Acetic acid	0.174	Hexane	0.020

(Kappe et al., 2009, p. 15)

Solvents can be classified as high ($\tan \delta > 0.5$), medium ($\tan \delta 0.1- 0.5$) and low ($\tan \delta < 0.1$) microwave absorbing. ($\tan \delta = \delta'' / \delta'$)



Absorption of MW by Vessels

Loss tangents ($\tan \delta$) of low-absorbing materials, 2.45 GHz, 25 °C

Material	$\tan \delta (\times 10^{-4})$	Material	$\tan \delta (\times 10^{-4})$
Quartz	0.6	Plexiglass	57
Ceramic	5.5	Polyester	28
Porcelain	11	Polyethylene	31
Phosphate glass	46	Polystyrene	3.3
Borosilicate glass	10	Teflon	1.5

(Kappe et al., 2009, p. 18)



Microwave vs conventional thermal heating

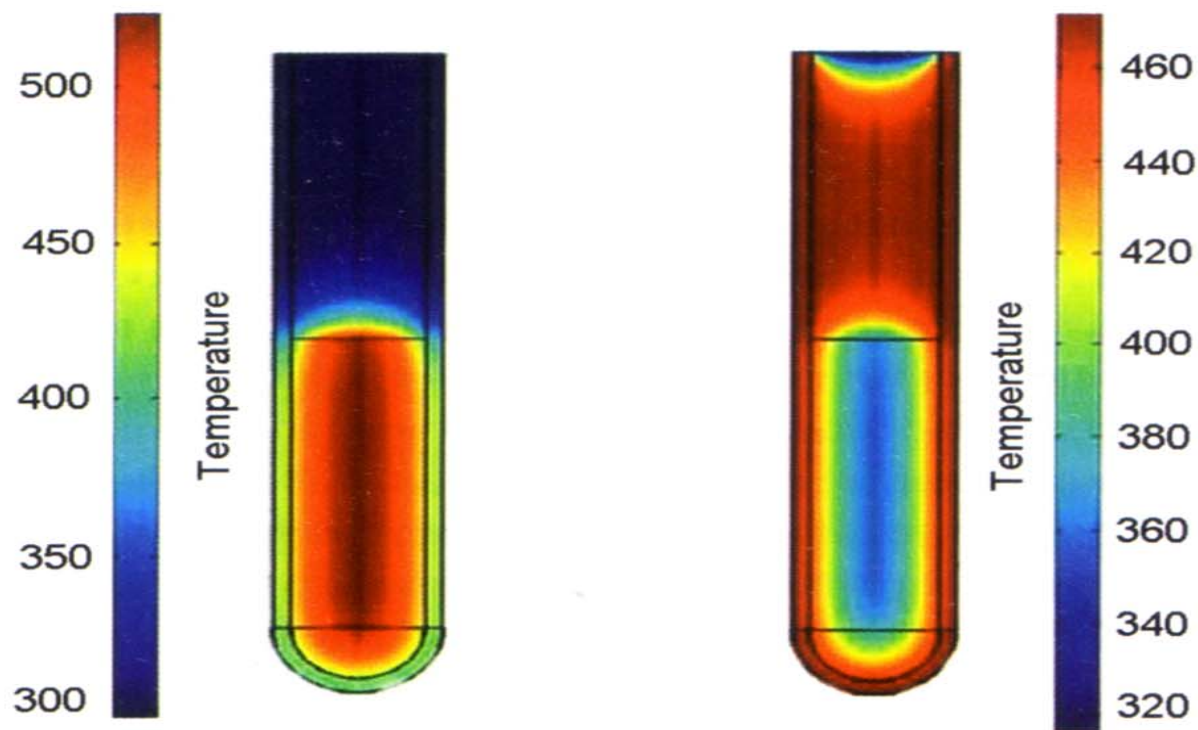


Fig. 2.6 Inverted temperature gradients in microwave versus oil-bath heating [12]. Temperature profiles (finite element modeling) after 1 min as affected by microwave irradiation (left) compared to treatment in an oil bath (right). Microwave irradiation raises the

temperature of the whole volume simultaneously (bulk heating), whereas in the oil-heated tube the reaction mixture in contact with the vessel wall is heated first. Temperature scales in Kelvin. Reproduced with permission from [12].



Super-heating

Solvent	B.p./ °C)	B.p. MW/°C	Difference
Water	100	105	5
Ethanol	79	103	24
Methanol	65	84	19
Dichloromethane	40	55	15
Tetrahydrofuran	66	81	15
Acetonitrile	81	107	26
Propan-2-ol	82	100	18
Acetone	56	81	25
Ethyl acetate	78	95	17
Dimethylformamide	153	170	17
Diglyme	162	175	13

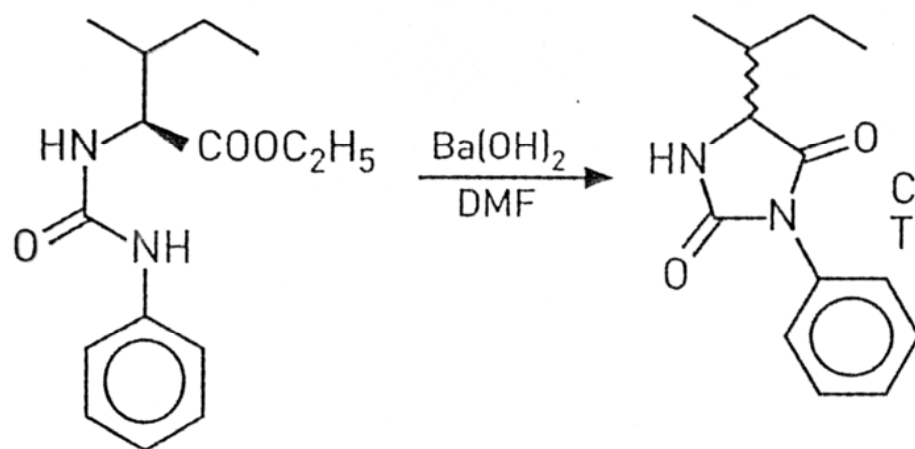


Examples in pharmaceutical chemistry

NEW DOORS

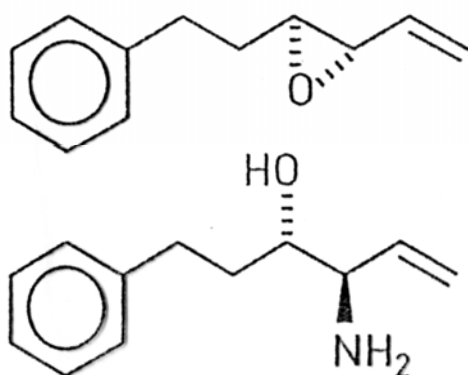
Microwave-based system may contribute to shorter drug development times

Hydantoin synthesis



Coherent Synthesis: 4 minutes, 90% yield
Traditional synthesis: 48 hours, 54% yield

Aminolysis

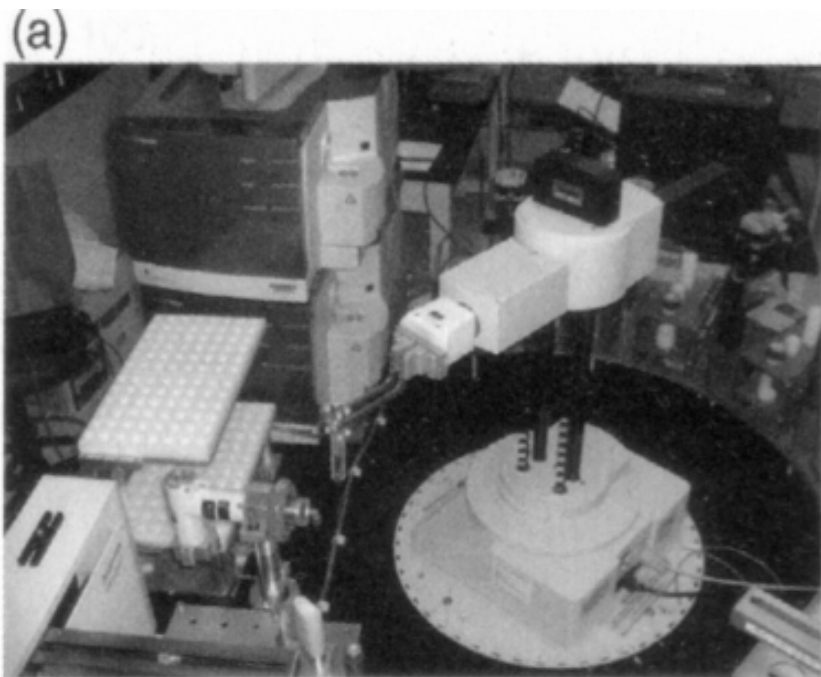


Coherent Synthesis: 7 minutes, 93% yield
Traditional chemistry: 240 hours, 13% yield

(C&EN, Feb, 11, 2002, pp. 17-18)



Robotic facility (Abbott Lab) (a) and high throughput factory (Novartis) (b)



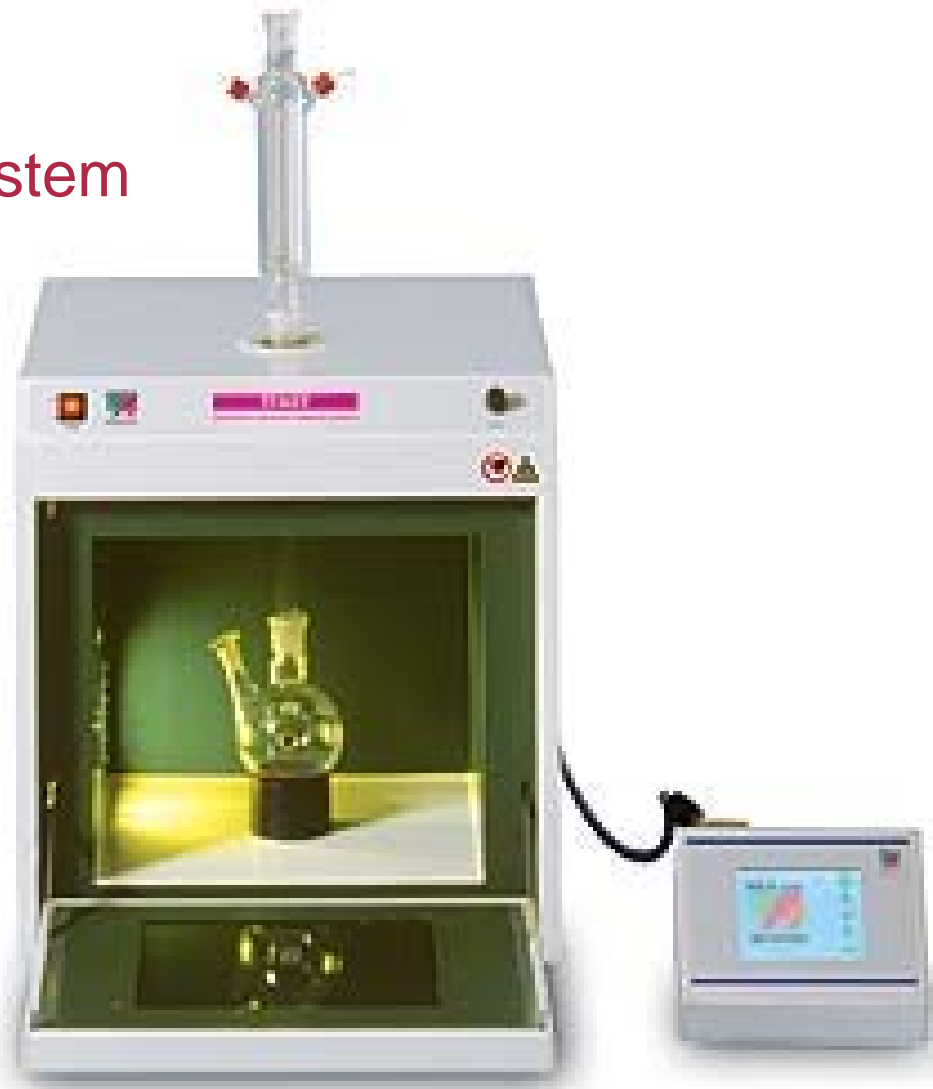
(Kappe, *et al.*, 2009, p. 117)



Laboratory scale preparations

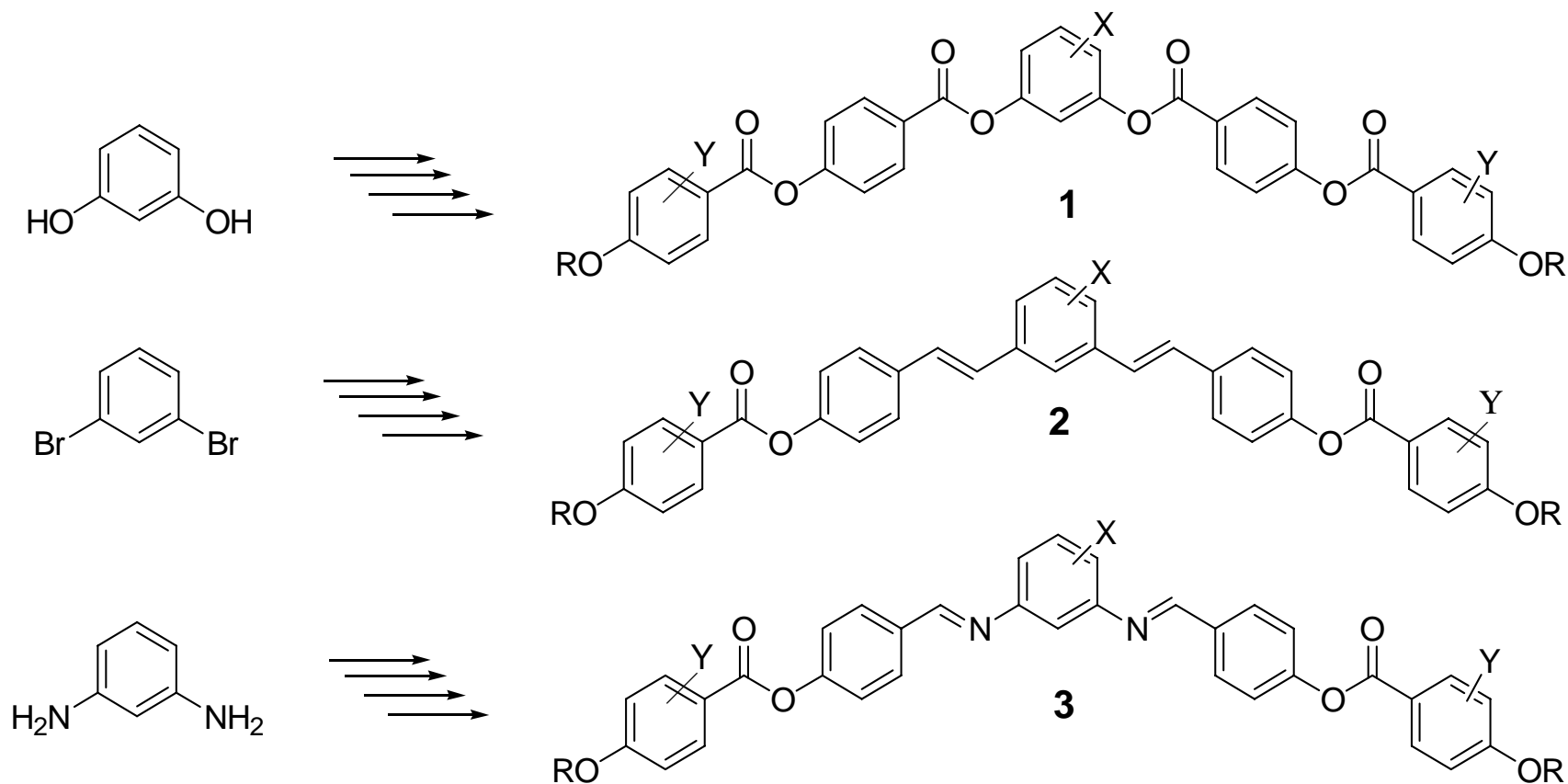
簡單型儀器

Milestone START System



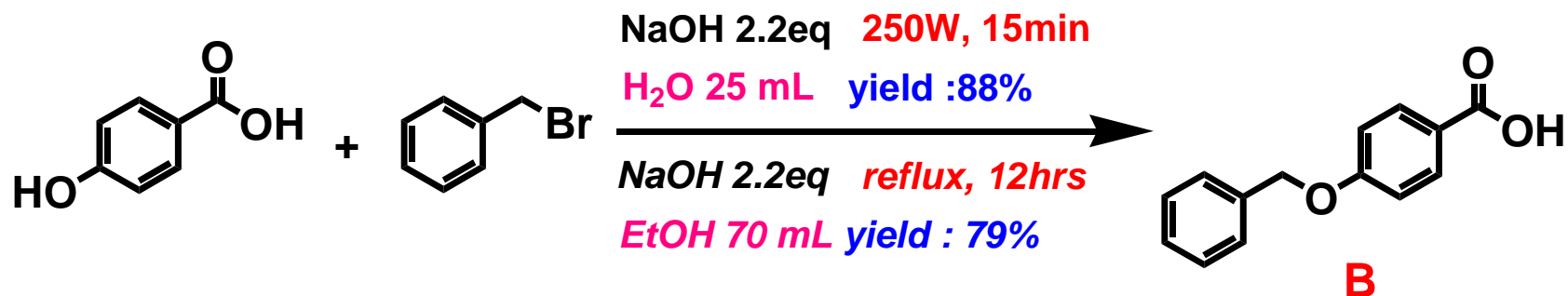
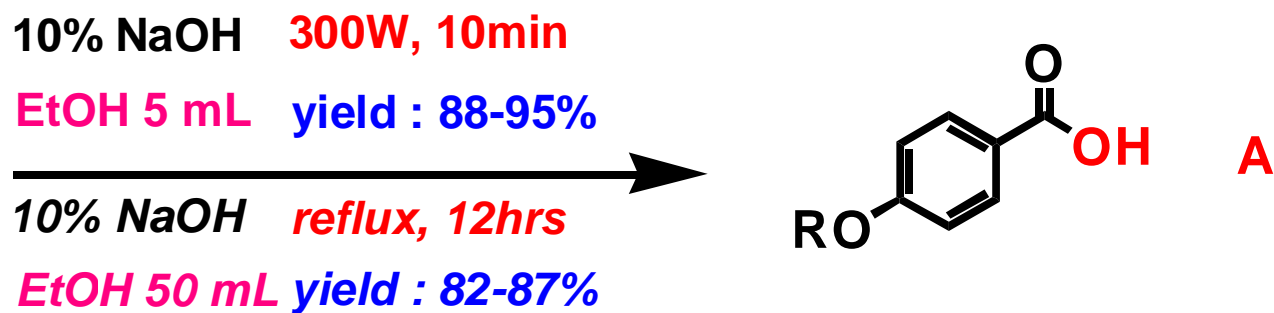
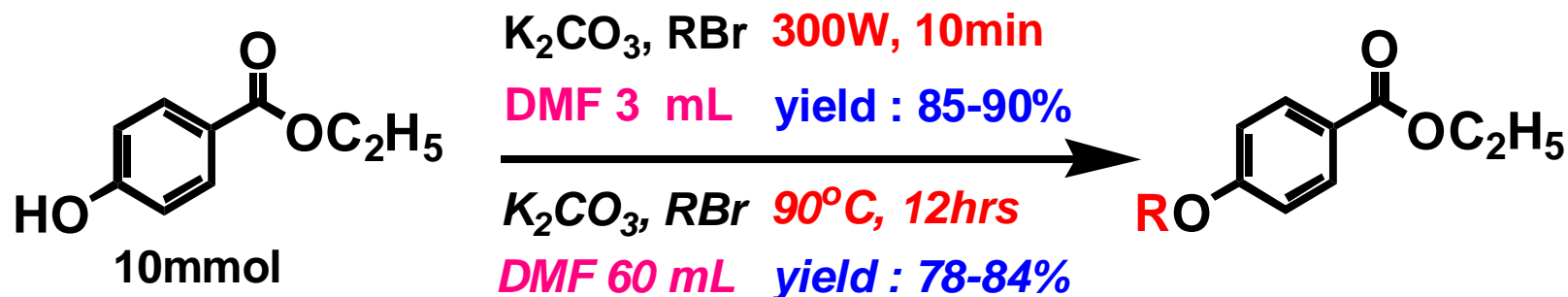


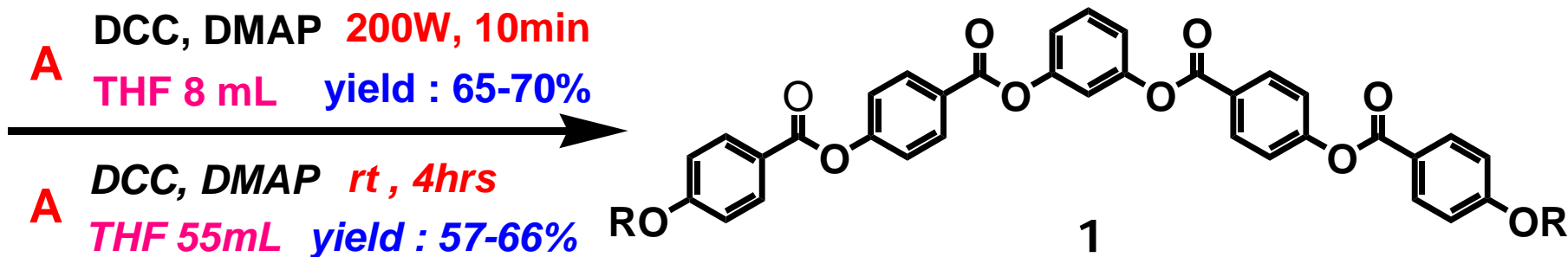
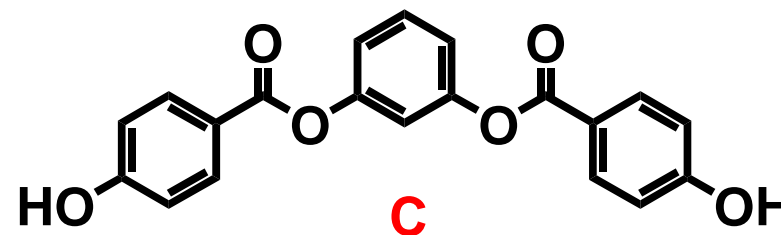
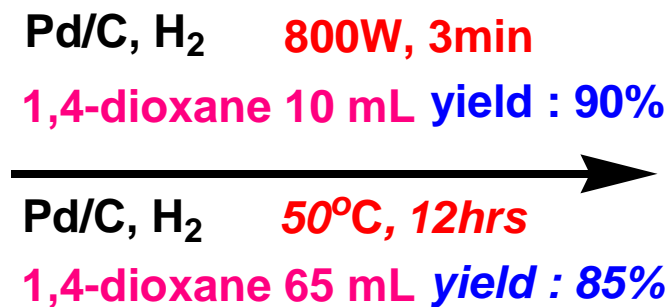
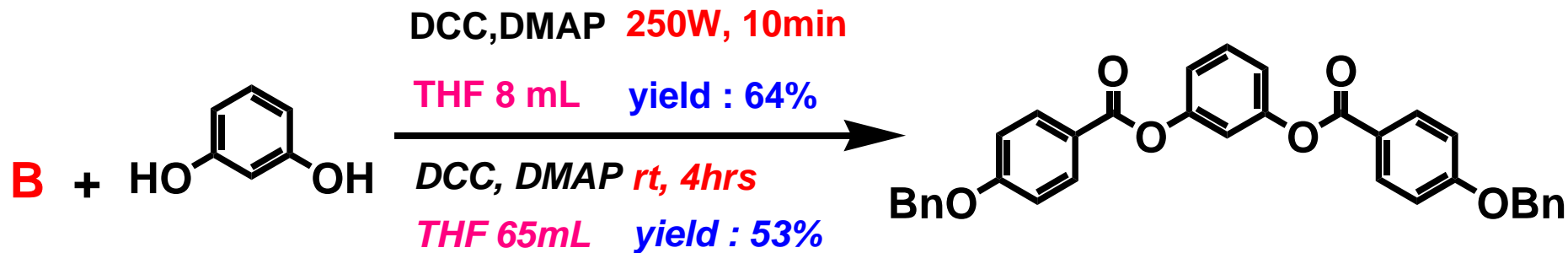
Microwave-assisted Organic Preparations of banana shape molecules

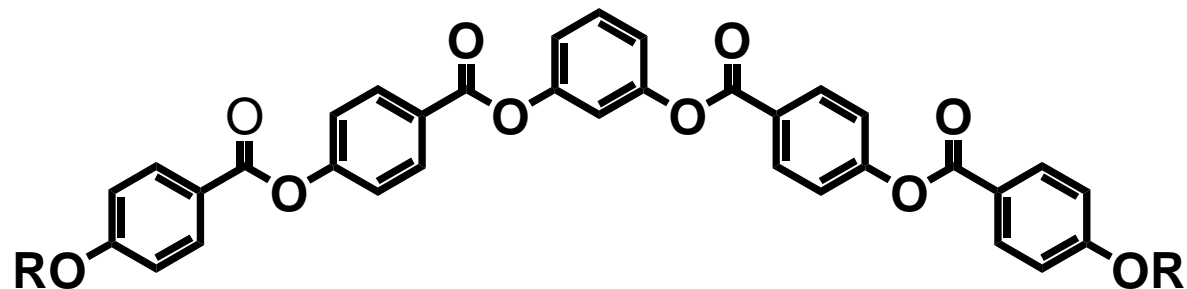


R = alkyl groups of different chain length

(Liu and coworkers, 2003-2006)







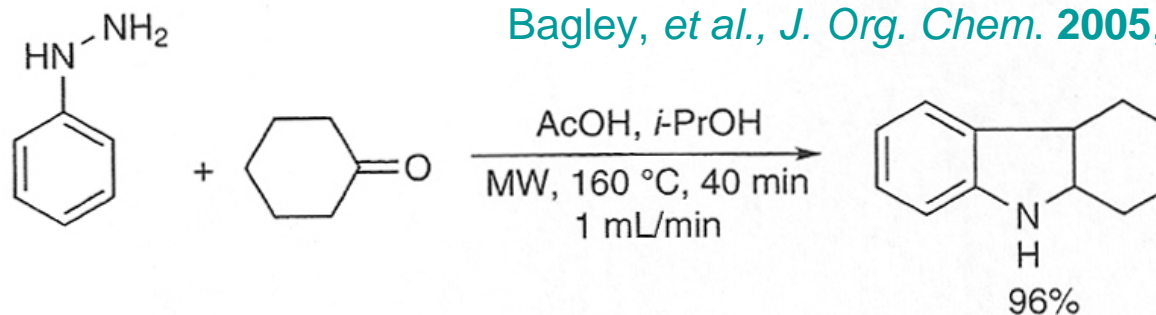
	MW	Traditional
Yield (6 steps from resorcinol)	33-35%	20-23%
Reaction time	58 min	56hrs
Solvent	34 mL	360 mL
Power (kW/hr)	0.85	2.0

微波反應法快捷, 節能, 高產率, 省溶劑, 選擇性好。
是極佳之永續化學製備方法。建議試用。

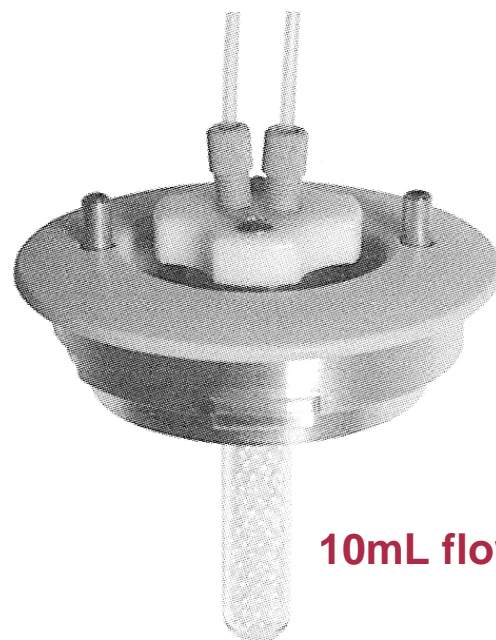


Fischer Indole synthesis with continuous flow mode to scale-up

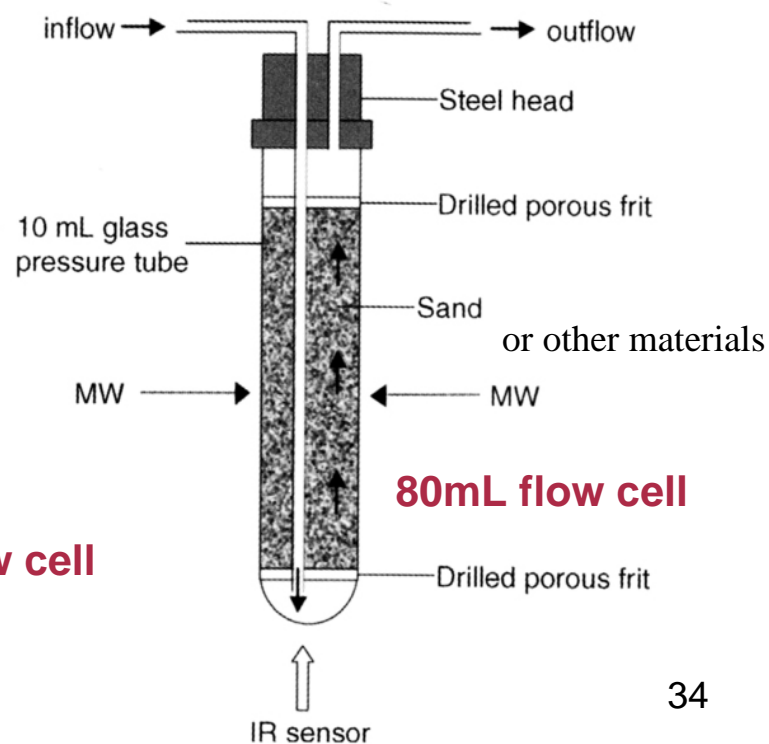
Bagley, *et al.*, *J. Org. Chem.* **2005**, *70*, 7003-7006



CEM Voyager_{CF}



10mL flow cell

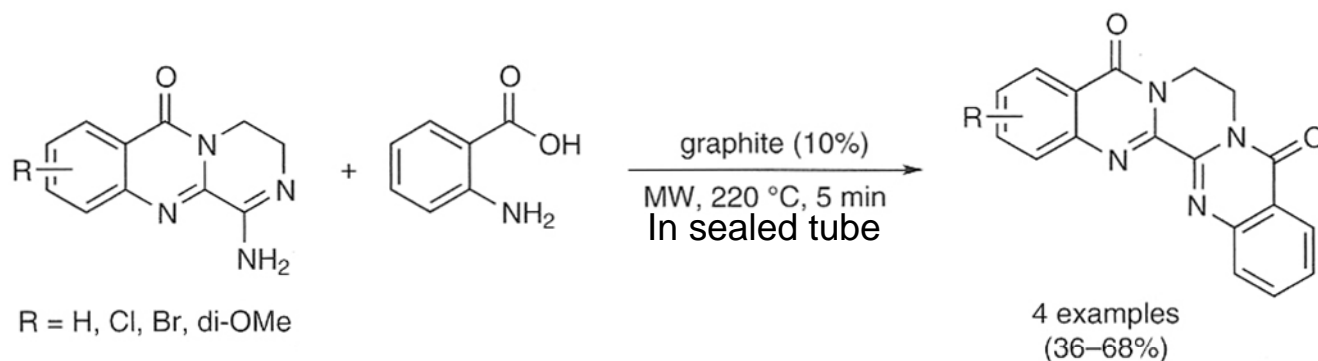




More examples

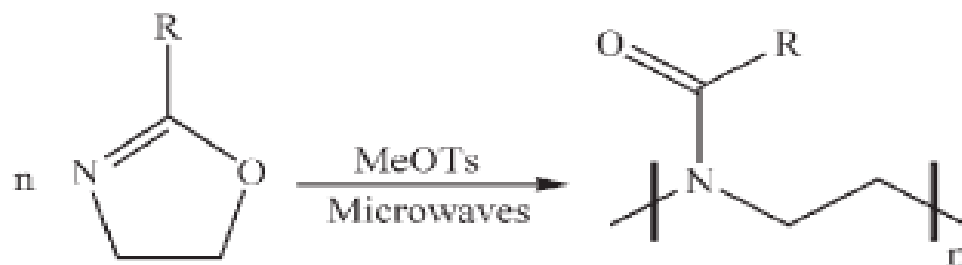
Solventless reaction using graphite as sensitizer

(**caution:** temperature may be very high, the use of quartz reactor is preferred)



Tetrahedron Lett. **2005**,
46, 3445-3447

Cationic ring-opening polymerization of 2-oxazolines (a review)



Yields were 10-20% higher
than thermal methods

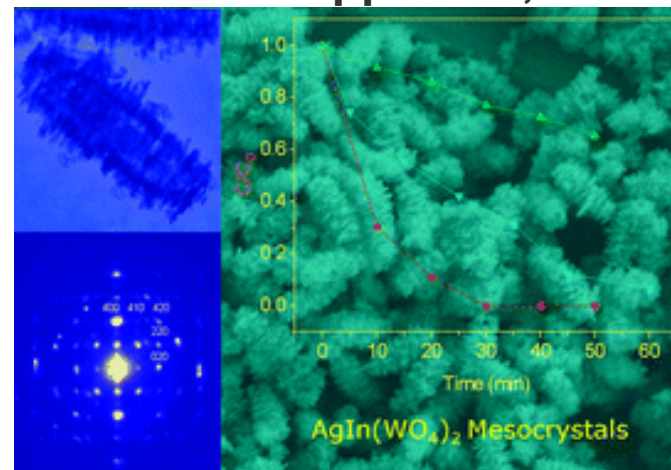
(Green Chem. **2007**, 9, 304-314)



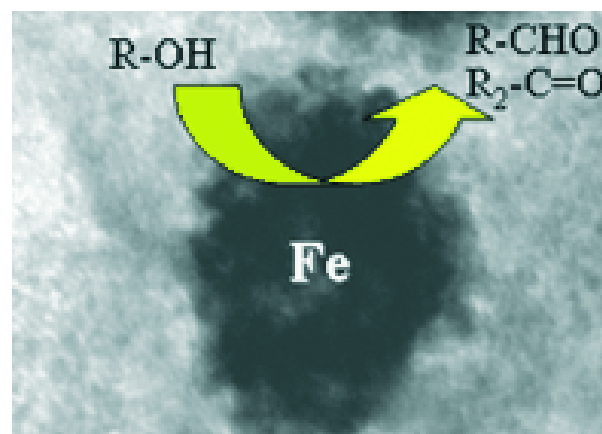
Efficient microwave preparations of mesocrystals and nanoparticles

A new kind of silver indium tungsten oxide ($\text{AgIn}(\text{WO}_4)_2$) mesocrystals with high hierarchy can be synthesized by a microwave-assisted approach, which shows high and selective photocatalytic activity for the degradation of different organic dyes under UV and visible light irradiation.

Hu, *et al. Chem. Commun.* **2010**, 46, 2277 - 2279



Highly active and stable iron nanoparticles have been prepared on a range of supports using a facile and environmentally friendly microwave approach. These inexpensive metallic iron nanoparticles were found to be extremely active and selective in the H_2O_2 oxidation of various alcohols (under 200W MW at 70-90°C for 1 hr), achieving excellent turnover numbers (more than 150).



González-Arellano, *et al., ChemSusChem* **2008**, 1, 746-750



Organic Process Research & Development **2010**, *14*, 351–361

Flow Processing of Microwave-Assisted (Heterogeneous) Organic Reactions

Mark H. C. L. Dressen,[†] Bastiaan H. P. van de Kruijs,[†] Jan Meuldijk,[‡] Jef A. J. M. Vekemans,[†] and Lumbertus A. Hulshof^{*†}
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Organic Process Research & Development **2010**, *14*, 205–214

Exploring the Scope for Scale-Up of Organic Chemistry Using a Large Batch Microwave Reactor

Jason R. Schmink, Chad M. Kormos, William G. Devine, and Nicholas E. Leadbeater^{*}
Department of Chemistry, University of Connecticut, 55 North Eagleville Road, Storrs, Connecticut 06269-3060, U.S.A

Organic Process Research & Development **2010**, *14*, 215–224

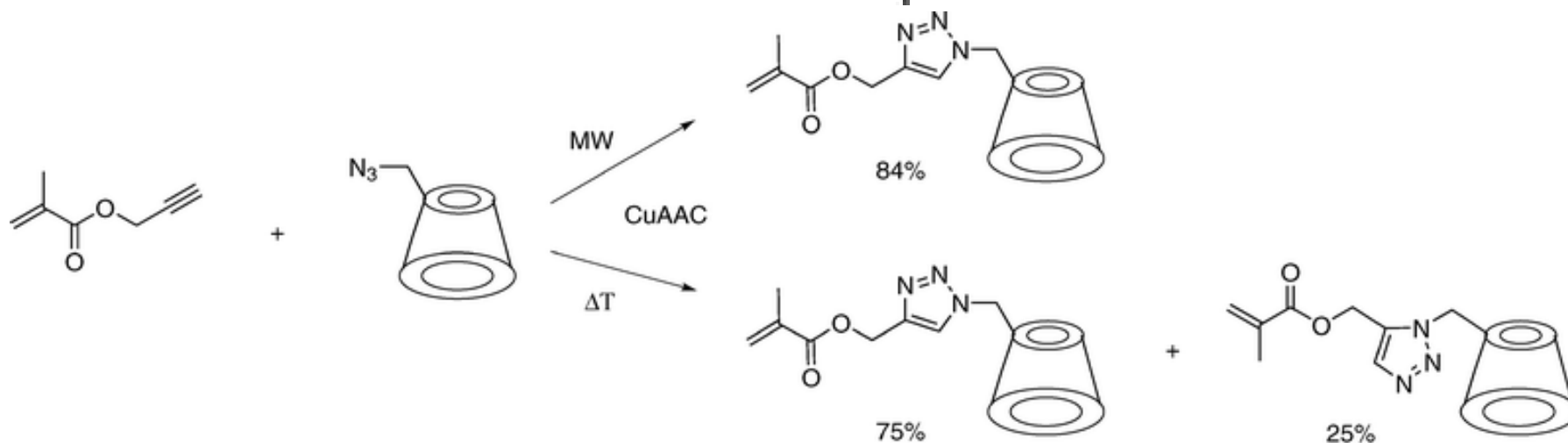
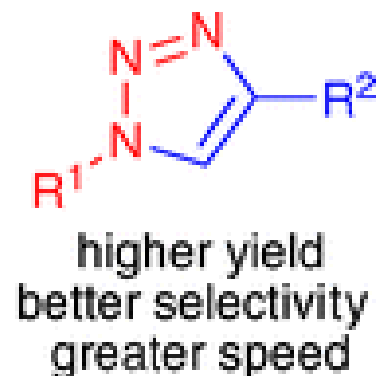
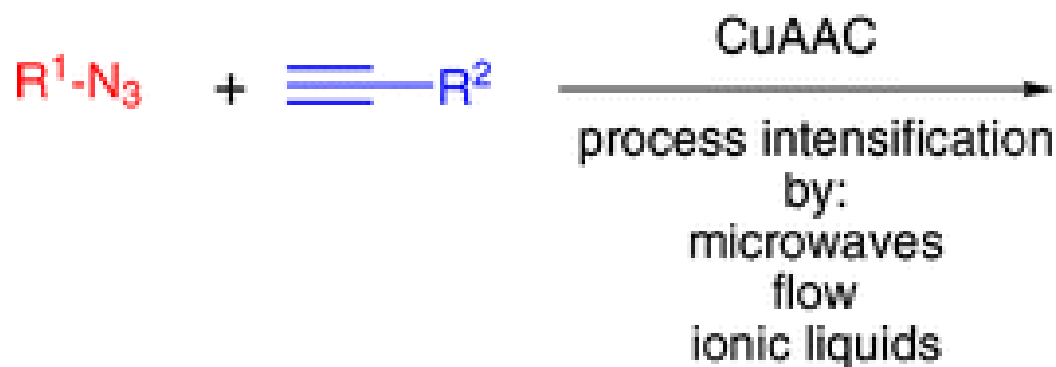
Translating High-Temperature Microwave Chemistry to Scalable Continuous Flow Processes

Markus Damm, Toma N. Glasnov, and C. Oliver Kappe^{*}
Christian Doppler Laboratory for Microwave Chemistry (CDLMC) and Institute of Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria



Click chemistry under non-classical reaction conditions

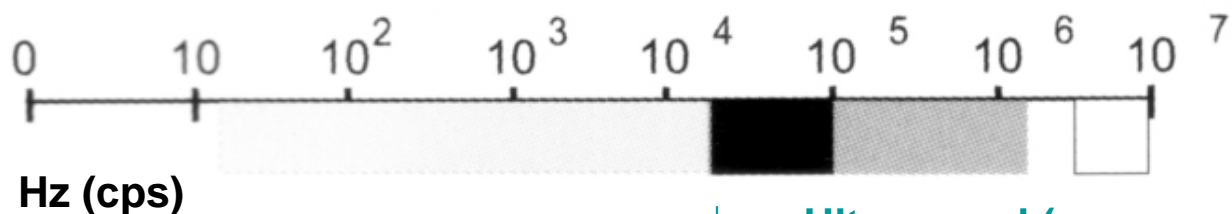
Kappe and Van der Eycken, *Chem. Soc. Rev.* **2010**, 39, 1280 - 1290





Sonochemistry

Sound frequencies



→ Ultrasound (supersound)

Human hearing



20Hz - 20kHz

(Normally, 16Hz to 16kHz)

Conventional power ultrasound



20kHz - 100kHz

high input power (1-1000 W/cm²)
(Destructive)

Extended range for sonochemistry



20kHz —2MHz

Diagnostic ultrasound



5MHz - 10MHz

Low input power (mW/cm²)

(Non-invasive)

Used for cleaning, chemical reactions, plastic welding, etc.

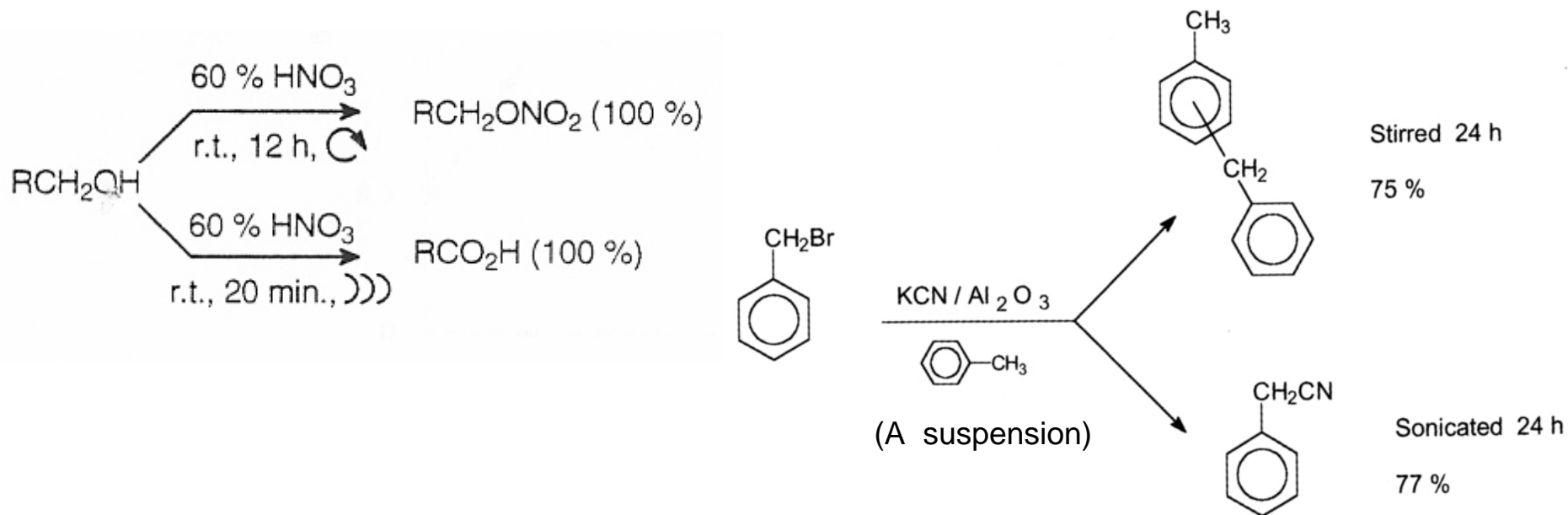
Mason, *Practical Sonochemistry: User's Guide to...*, 2nd Ed, E. Horwood, 2001

Mason and Lorimer, *Applied Sonochemistry*, Wiley-VCH, 2002

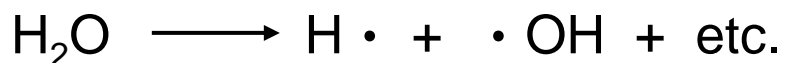


Sonochemical switching of pathways

For **true** sonochemical reactions (homogeneous or heterogeneous), formation of radical or radical-ion will be favored by ultrasound. But **false** sonochemical reactions (heterogeneous) are influenced by physical and mechanical properties of sonication (ultrasound agitation). Examples are:



Sonochemical decomposition pathway of water into radicals





Promoting emulsion and suspension polymerizations

Ultrasonic waves have also been found to increase the rates of emulsion and suspension polymerisations. For example, we have found a twofold increase in the thermally initiated production of polystyrene by emulsion polymerisation when in the presence of ultrasound (20 kHz). Possible explanations for these increases include:

- (i) the oxidation of impurities (see above),
- (ii) the removal of oxygen (known to inhibit radical reactions) by ultrasonic degassing, and
- (iii) ultrasonic degradation of the polymer to provide more active sites (i.e. autocatalysis).

Cleaner with timer and heater



Less expensive

ultrasound horn



more effective

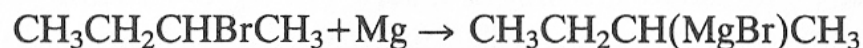


Heterogeneous reactions in a cleaning bath



Formation of Grignard reagents

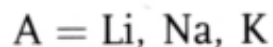
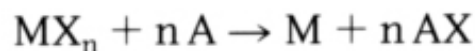
(Mason and Lorimer, p. 98)



Type of diethyl ether used	Method	Induction time
<u>Pure, dried</u> (0.01% water) (0.01% ethanol)	Stirred	6–7 min
<u>Reagent grade</u> (0.5% water) (2.0% ethanol)	Sonicated	less than 10 s
	Stirred	2–3 h (<i>crushed</i>)
	Sonicated	3–4 min

Generation of metal (Cu, Ni, etc.) powders

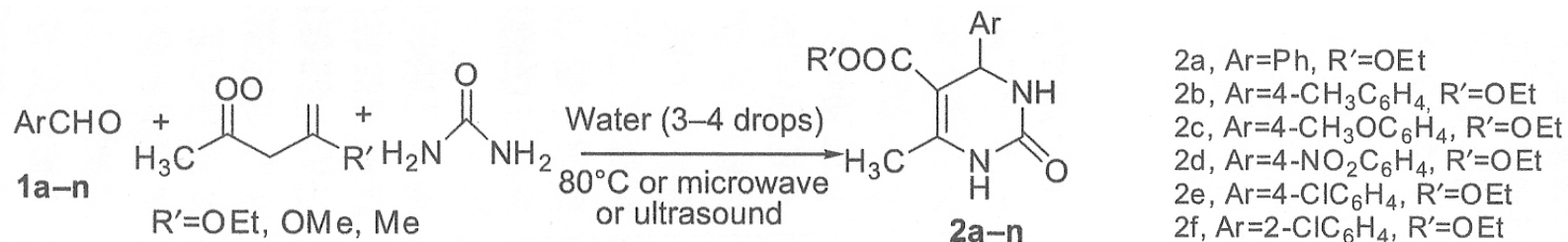
(Mason and Lorimer, p. 95)



Method	Time
$\text{CuI}_2 + \text{K}$ reflux in THF	8 h
$\text{CuBr}_2 + \text{Li}$ ultrasonic bath at 25 °C in THF	less than 40 min
$\text{NiCl}_2 + \text{Li}$ (powder) stir at 25 °C	14 h
$\text{NiCl}_2 + \text{Li}$ (powder) stir in ultrasonic bath at 25 °C	less than 40 min



Synthesis of 3,4-dihydropyrimidinones under solvent-free conditions. Comparison of conventional heating, microwave and ultrasound irradiation



Entry	Product 2	Conventional ^b		Microwave ^c	Ultrasound ^d	
		t (min)	Yield ^e	Yield ^e	t (min)	Yield ^e
1	2a	45	92	98	30	96
2	2b	45	94	96	30	95
3	2c	50	90	96	35	92
4	2d	60	89	97	40	92
5	2e	65	90	96	40	94
6	2f	60	90	95	40	94
7	2g	55	80	88	35	85
8	2h	60	80	90	35	90
9	2i	75	92	90	50	82
10	2j	55	90	92	40	90
11	2k	60	92	95	35	94
12	2l	65	92	89	40	86
13	2m	60	90	90	35	87
14	2n	75	90	92	40	90

^aReaction conditions: aldehyde (2 mmol); urea (2 mmol); β-dicarbonyl compound (2 mmol); and water (3–4 drops).

^bHeating at 80°C.

^cMicrowave irradiation (750 W, reaction time 2 min).

^dUltrasound irradiation (25 kHz).

^eIsolated yields.

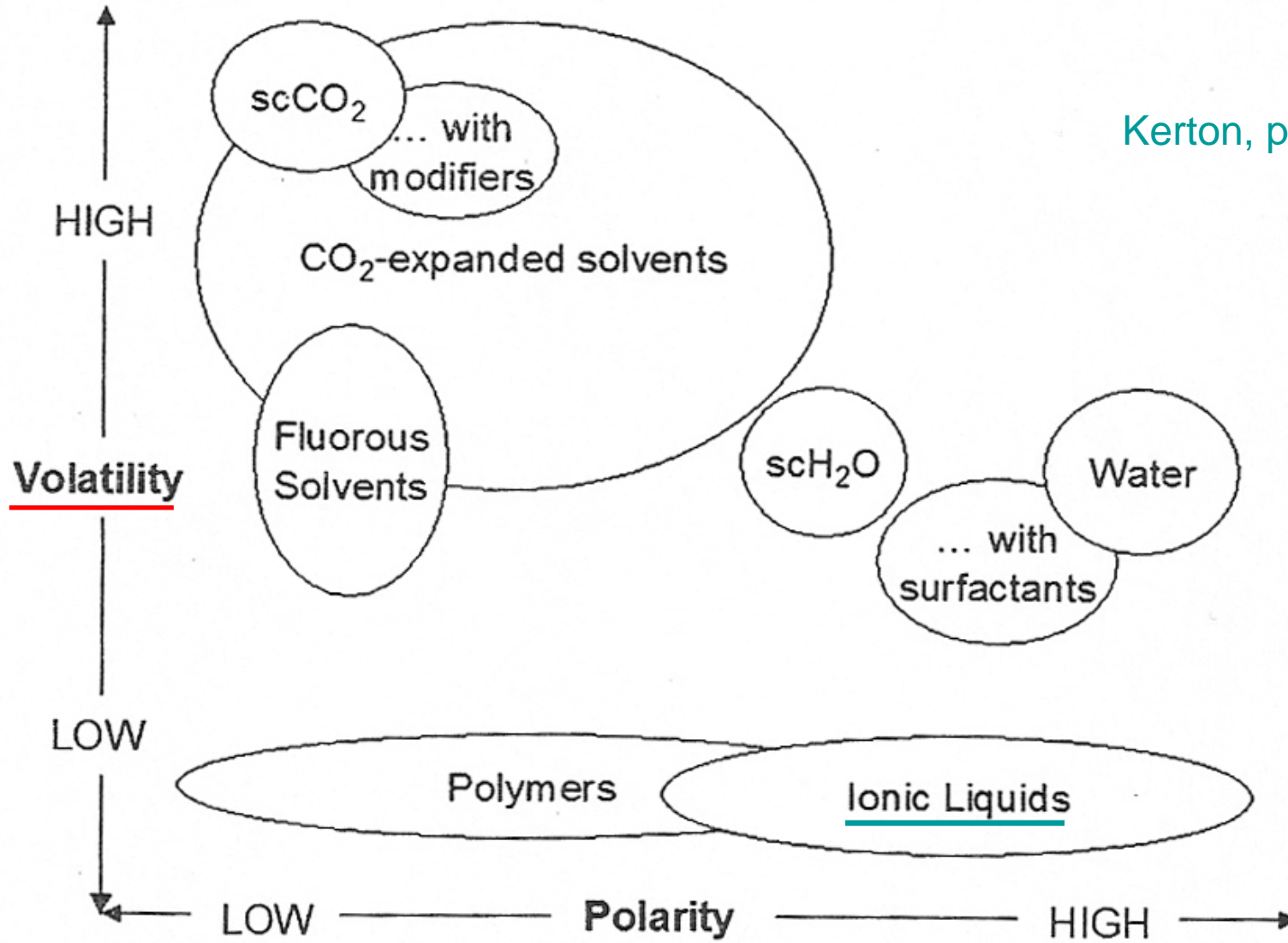
Green Chem. Lett. Rev. **2010**, *3*, 23-26.



Alternative solvents

Polarity and volatility characteristics

Kerton, p. 17





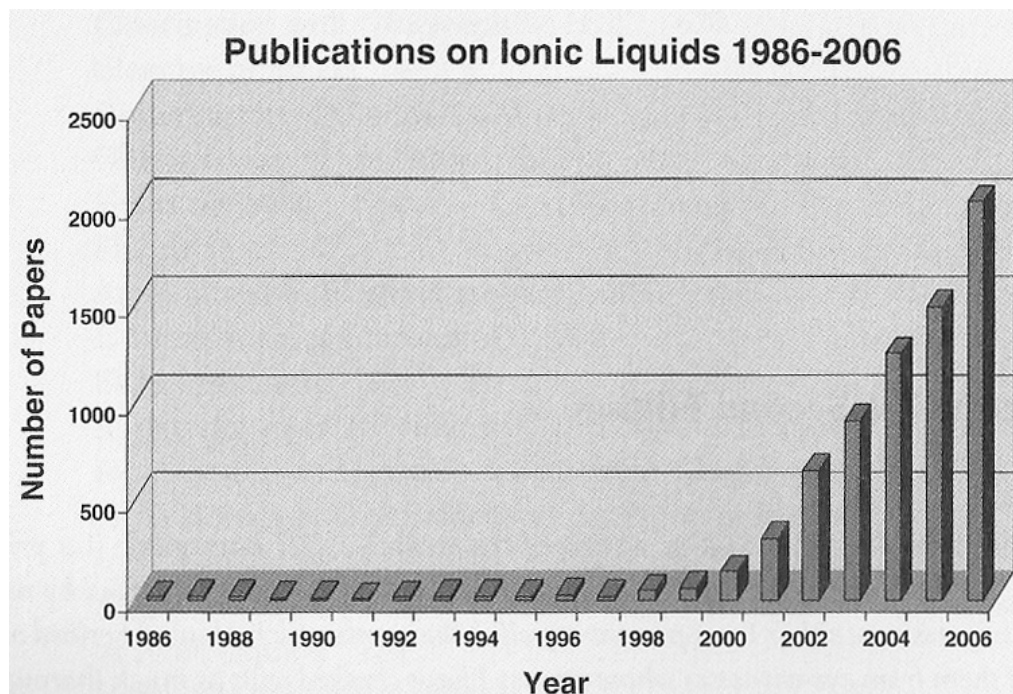
Ionic liquids in Synthesis

Ionic Liquids in Organic Synthesis, Ed. by Malhotra, ACS Symposium Series 950, **2006**

Ionic Liquids in Synthesis, 2nd, Completely Revised and Enlarged Edn., 2 Vols, Ed by Wasserscheid and Welton, Wiley-VCH, **2008**

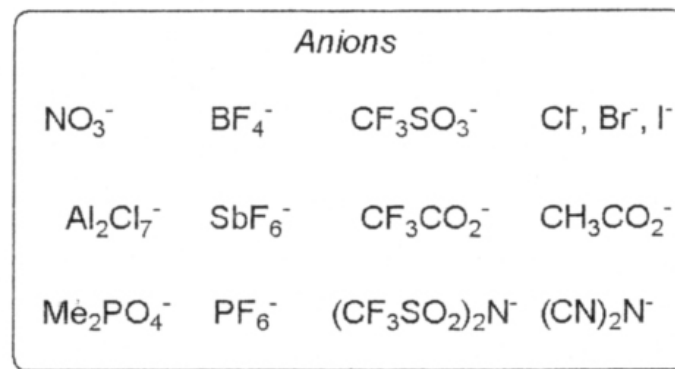
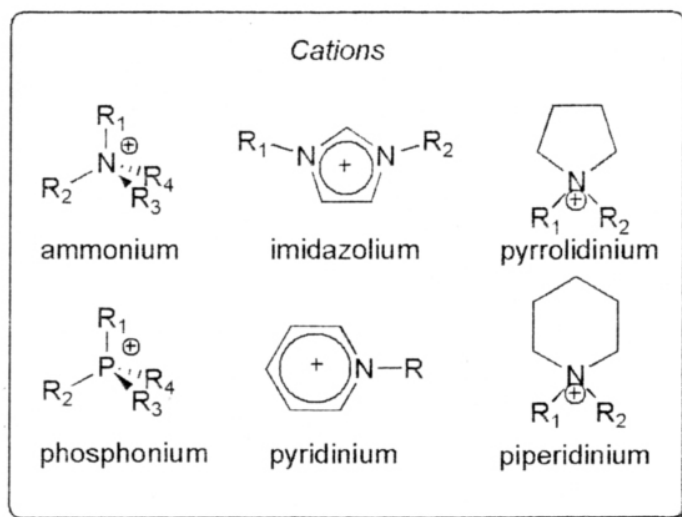
Alternative Solvents for Green Chemistry, by Kerton, RSC, Chapter 6, **2009**

Parvulescu and Hardacre, *Chem. Rev.* **2007**, 107, 2615-2665 (**Catalysis in Ionic Liquids**)





Room temperature ionic liquids



$R = (\text{CH}_2)_n\text{CH}_3, n = 1, 3, 5, \dots$

Table 6.1 Some physical properties of imidazolium-based ionic liquids.

Cation	Anion	Mp/ $^\circ\text{C}$	Thermal stability/ $^\circ\text{C}$	Density/ g cm^{-3}	Viscosity/ cP	Conductivity/ $\text{ohm}^{-1} \text{cm}^{-1}$
Emim	BF_4^-	6	412	1.24	37.7	1.4
Bmim	BF_4^-	-81	403	1.12	219	0.173
Bmim	$(\text{CF}_3\text{SO}_2)_2\text{N}^-$	-4	439	1.429	52	0.39
Bmim	PF_6^-	-61	349	1.36	450	0.146
Hmim	PF_6^-	-61	417	1.29	585	-

^aEmim = 1-ethyl-3-methylimidazolium, Bmim = 1-butyl-3-methylimidazolium, Hmim = 1-hexyl-3-methylimidazolium

(Kerton, p. 119)



Properties

- Liquid range of 300°C (−96–+200°C) (It is distillable)
- Excellent solvents for organic, inorganic, and polymeric materials
- Acidic compositions are superacids ($pK_a \approx -20$)
- Some are very water sensitive and must be used in a dry box; others are hydrophobic and air stable
- Thermally stable under conditions up to 200°C
- *Now* — easy to buy and simple to prepare
- *No* measurable vapor pressure at room temperature
- Nonflammable (but some are explosive!)
- Exhibit Brønsted, Lewis, Franklin, and “super” acidity
- *Highly* solvating—therefore low volumes used, thus process intensification
- Catalysts as well as solvents
- Highly selective reactions
- *New chemistry*

Some are corrosive, and some are harmful

Mostly non-biodegradable



Some safety data

	BMIM Cl ^a	EMIM EtOSO ₃ ^b	MTEOA MeOSO ₃ ^c
Acute oral toxicity	toxic	not harmful	not harmful
Skin irritation	irritant	non-irritant	non-irritant
Eye irritant	irritant	non-irritant	non-irritant
Sensitization	non-sensitizing	non-sensitizing	non-sensitizing
Mutagenicity	non-mutagenic	non-mutagenic	non-mutagenic
Biological degradability	not readily degradable	not readily degradable	readily biodegradable
Toxicity to daphniae	autelytoxic	acutely not harmful	acutely not harmful
Toxicity to fish	acutely not harmful	—	acutely not harmful

^aBMIM Cl = 1-Butyl-3-methylimidazolium chloride.

^bEMIM EtOSO₃ = 1-Ethyl-3-methylimidazolium ethylsulfate.

^cMTEOA MeOSO₃ = Tris-(2-hydroxyethyl)-methylammonium methylsulfate.

Ionic Liquids in Synthesis (Vol. 2), p. 683



Designing Sustainable Ionic Liquids

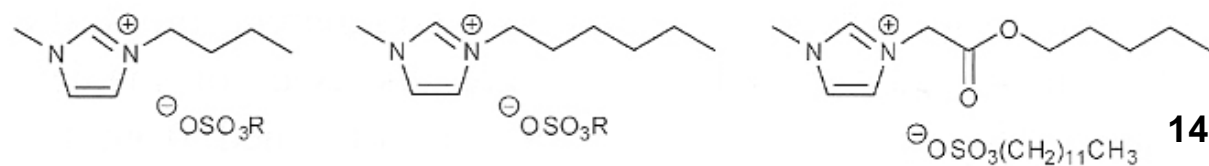


Ultimate goal: **Non-toxic and/or biodegradable**

(Ranke, *et al.*, *Chem. Rev.* **2007**, *107*, 2183-2206

Harjani, *et al.*, *Green Chem.* **2008**, *10*, 436-438; **2009**, *11*, 821-829)

Table 1 Percentage biodegradation of alkyl sulfates based on [bmim] and [hmim] cations after 28 days as determined by the CO₂ headspace test (ISO 14593)



12a R = (CH₂)₅CH₃
12b R = (CH₂)₆CH₃
12c R = (CH₂)₇CH₃
12d R = (CH₂)₈CH₃
12e R = (CH₂)₉CH₃
12f R = (CH₂)₁₁CH₃

13a R = (CH₂)₅CH₃
13b R = (CH₂)₆CH₃
13c R = (CH₂)₇CH₃
13d R = (CH₂)₈CH₃
13e R = (CH₂)₉CH₃
13f R = (CH₂)₁₁CH₃

Entry	No.	Compound ^a	Biodegradation (%)
1	12a	[bmim] [C ₆ H ₁₃ OSO ₃]	34
2	12b	[bmim] [C ₇ H ₁₅ OSO ₃]	36
3	12c	[bmim] [C ₈ H ₁₇ OSO ₃]	40
4	12d	[bmim] [C ₉ H ₁₉ OSO ₃]	47
5	12e	[bmim] [C ₁₀ H ₂₁ OSO ₃]	54
6	12f	[bmim] [C ₁₂ H ₂₅ OSO ₃]	58
7	13a	[hmim] [C ₆ H ₁₃ OSO ₃]	30
8	13b	[hmim] [C ₇ H ₁₅ OSO ₃]	33
9	13c	[hmim] [C ₈ H ₁₇ OSO ₃]	38
10	13d	[hmim] [C ₉ H ₁₉ OSO ₃]	36
11	13e	[hmim] [C ₁₀ H ₂₁ OSO ₃]	44
12	13f	[hmim] [C ₁₂ H ₂₅ OSO ₃]	49
13	14	[⁻ ester'-mim] [C ₁₂ H ₂₅ OSO ₃]	72

^a IL concentration = 40 mg L⁻¹.

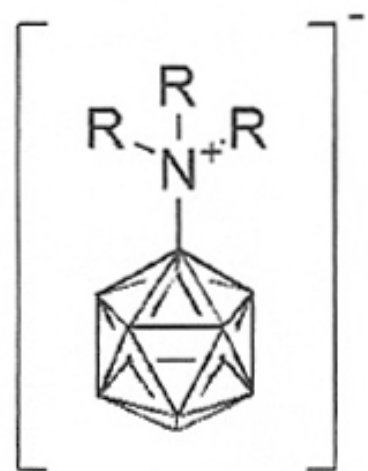


New ionic liquid with new type of anions

High chemical and physical **stability**, **non-corrosive**, **similar toxicity** to other widely used ILs.

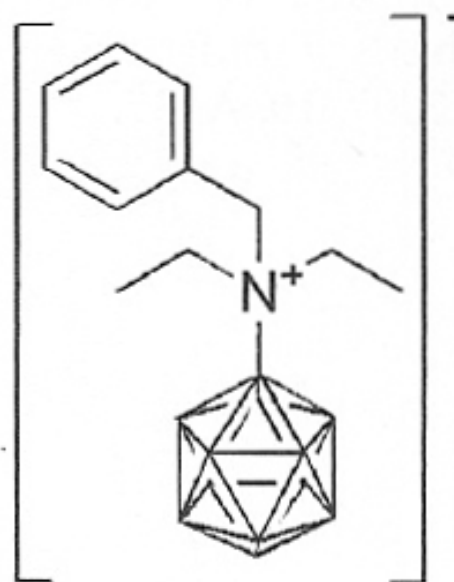
(Schaffran, *et al.*, *Green Chem.* **2009**, *11*,1458-1464)

symmetric substitution



R = CH₃ - C₆H₁₃

asymmetric substitution



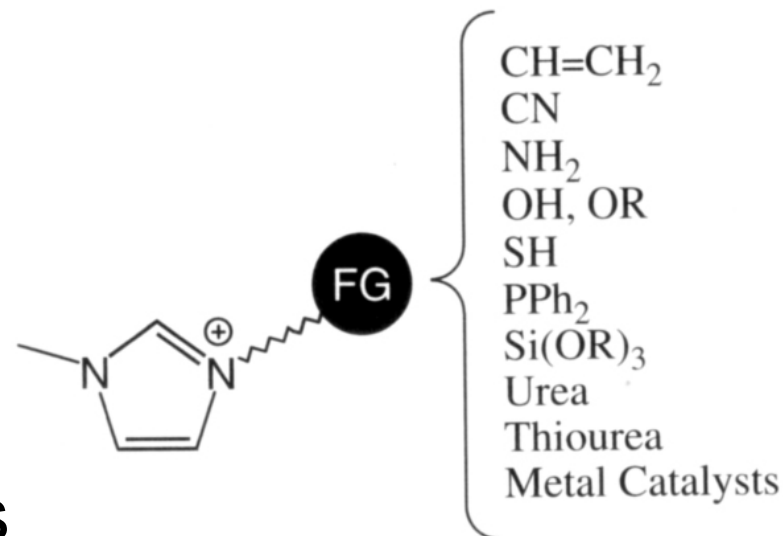
N,N,N-trialkylammoniumundecahydrododecaborates (-)



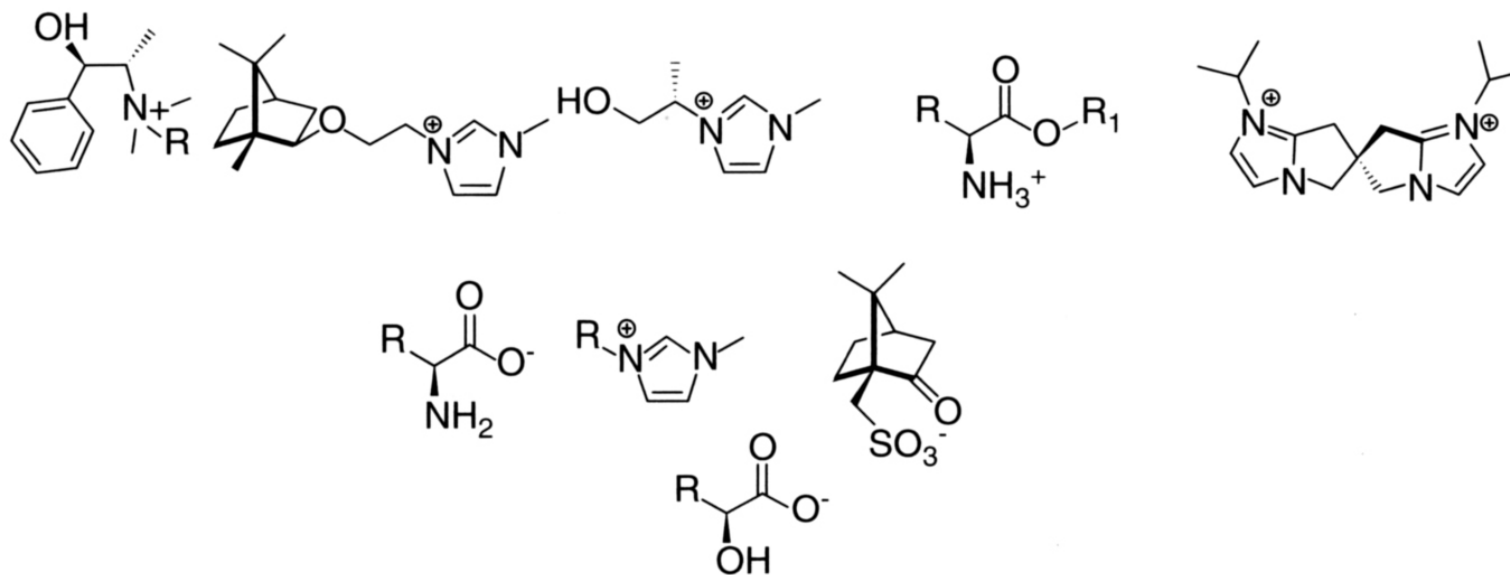
Task-specific ionic liquids

(Ballini (Ed), *Eco-Friendly Synthesis of Fine Chemicals*, Chapter 4, RSC, 2009)

Functionalized ionic liquid cations



Novel chiral ionic liquids





Lipidlike Ionic Liquids

(Murray, *et al. Angew. Chem. Int. Ed.* **2010**, *49*, 2755-2758)

Ionic liquids (ILs) with long, unsaturated alkyl appendages (see top structure) defy established trends that link long ion-bound alkyl groups to higher melting points. The new ILs are also less viscous than a saturated standard (see bottom structure) at the same temperature.

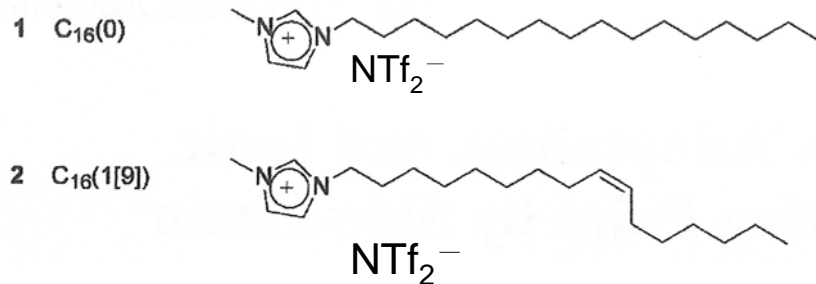
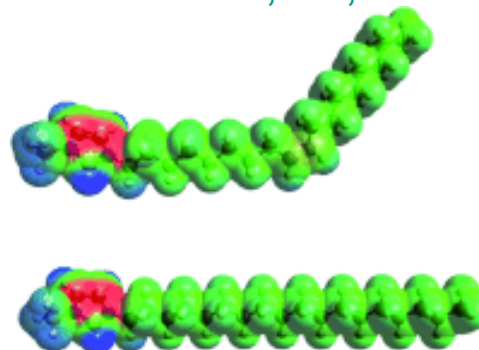


Table 1: T_m values of lipid-inspired ILs and related compounds.

IL	Alkyl group ^[a]	T_m [°C]	T_m (fatty acid) [°C] ^[b]	T_m (methyl ester) [°C]
1	C ₁₆ (0)	46.9	63.5	33.5
2	C ₁₆ (1[9])	-22.0	0.5	-33.9
3	C ₁₈ (0)	53.5	69.6	38.9
4	C ₁₈ (1[9])	-20.9	16.2	-19.6
5 ^[c]	C ₁₈ (1[11])	-9.8	12.0	-
6	C ₁₈ (1[9t])	16.0	43.7	10.3
7	C ₁₈ (2[9,12])	-46.8	-6.5	-35.0
8	C ₂₀ (0)	62.5	75.5	54.0
9 ^[d]	C ₂₀ (1[11])	4.2	23.5	-34.0
10	C ₁₀ (0)	-18.9	31.0	-12.5
11b	C ₁₀ (1[4])	-37.0	-	-



Applications

Friedel-Crafts reactions

Coupling reactions

Oxidation

Reduction

Sulfonation

Nitration

Halogenation

Diazotization

Diels-Alder reaction

Aldol condensation

Formation of Coordination compounds

Formation of inorganic oxides

Oligomerization

Polymerization

Bio-catalytic reactions

N- and O-alkylations

Chiral hydrogenation

Nanoscale process

and many more

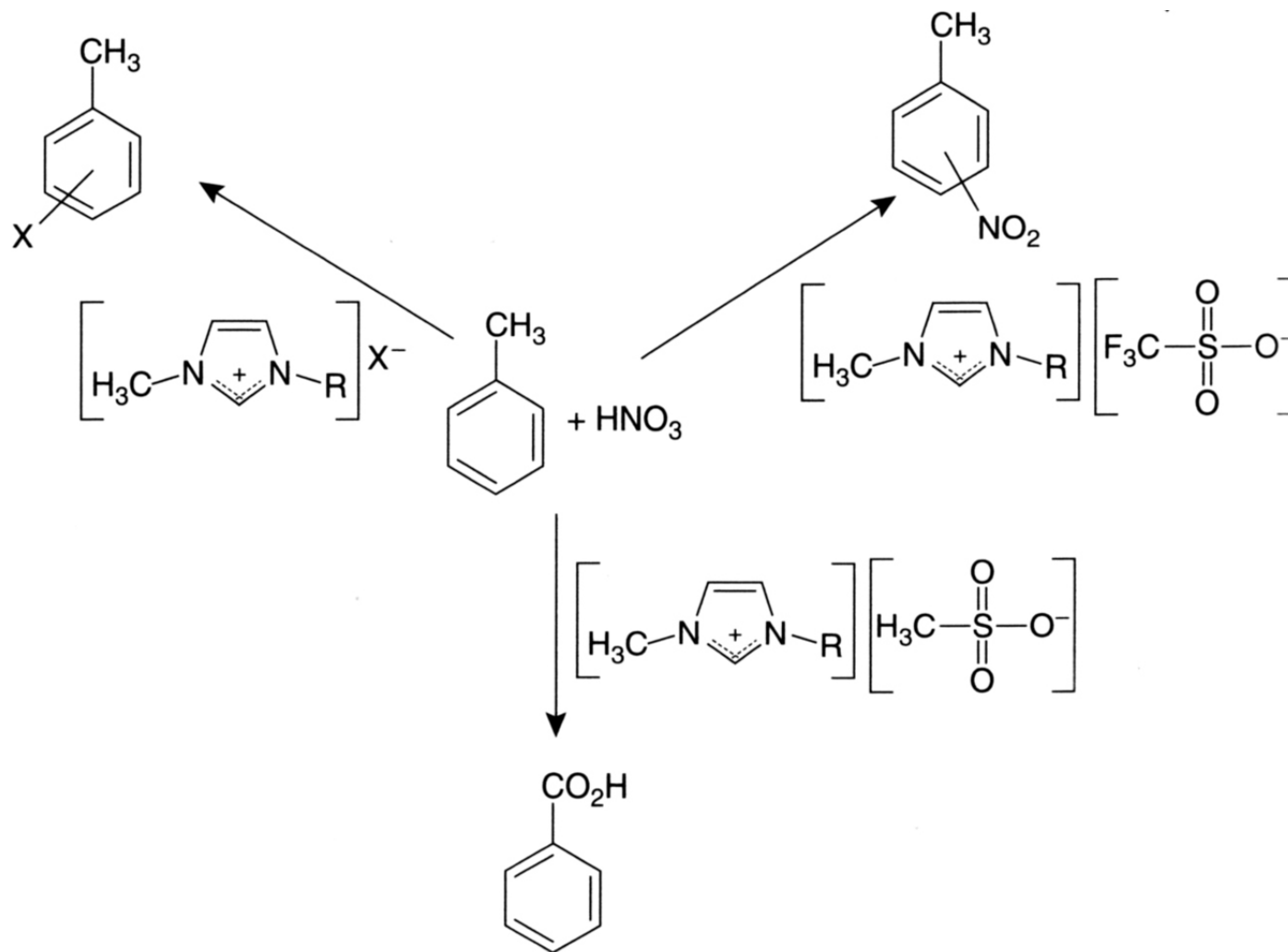
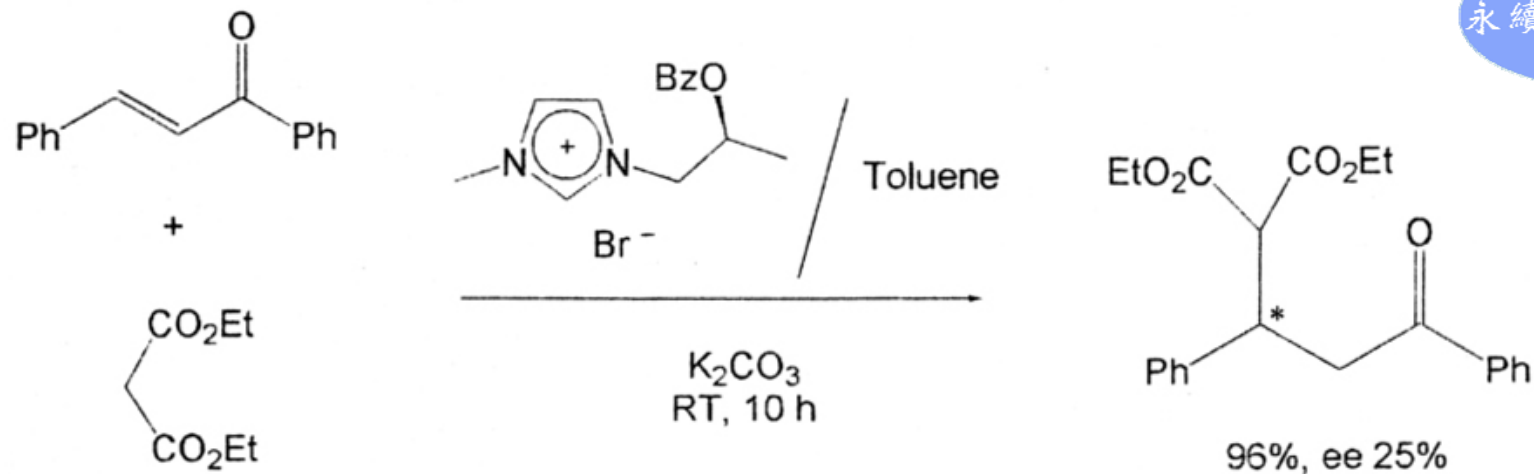


Figure 5.8 The reactions between toluene and nitric acid in (a) a halide-based ionic liquid, (b) a triflate-based ionic liquid, and (c) a mesylate-based ionic liquid.

(Methods and Reagents for Green Chemistry, p. 119, Wiley, 2007)



a)



b)

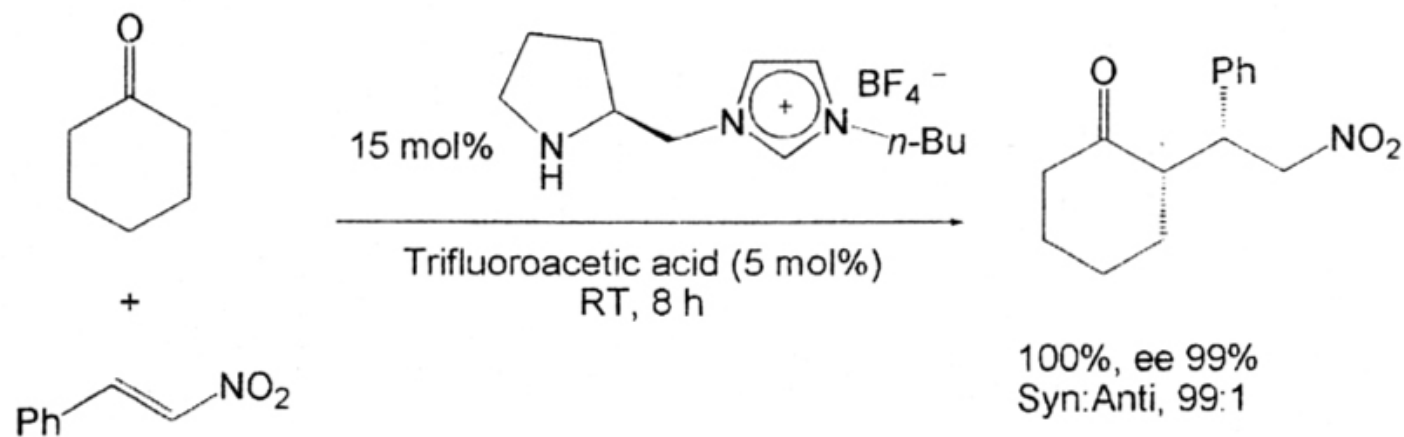


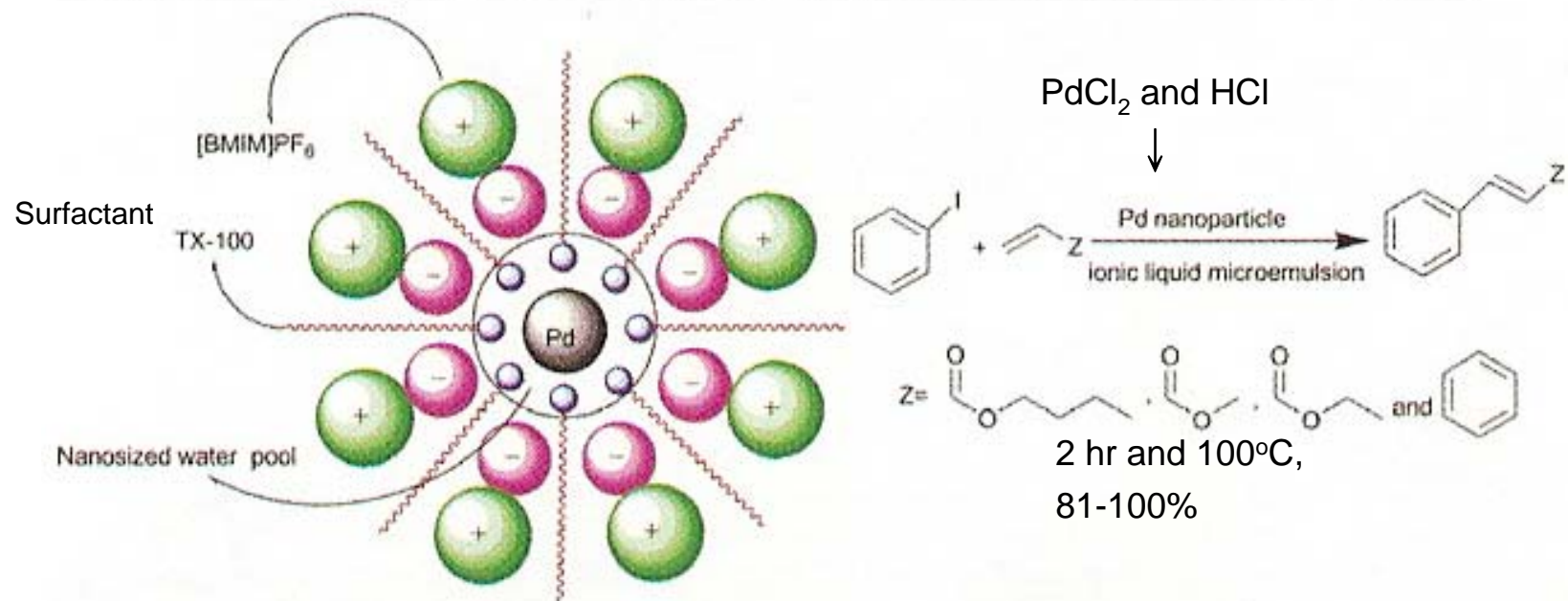
Figure 6.8 Asymmetric Michael addition reactions using chiral ionic liquids: (a) derived from lactate, (b) derived from proline.



Pd nanoparticles catalyzed ligand-free Heck reaction in ionic liquid microemulsion

Guoping Zhang, Haihui Zhou,* Jiaqi Hu, Mei Liu and Yafei Kuang*

In the H₂O/TX-100/[BMIM]PF₆ microemulsion, palladium nanoparticles were prepared *in situ* for the first time, and the resultant Pd catalysts exhibited high efficiency for Heck reaction without the aid of phosphine ligands.



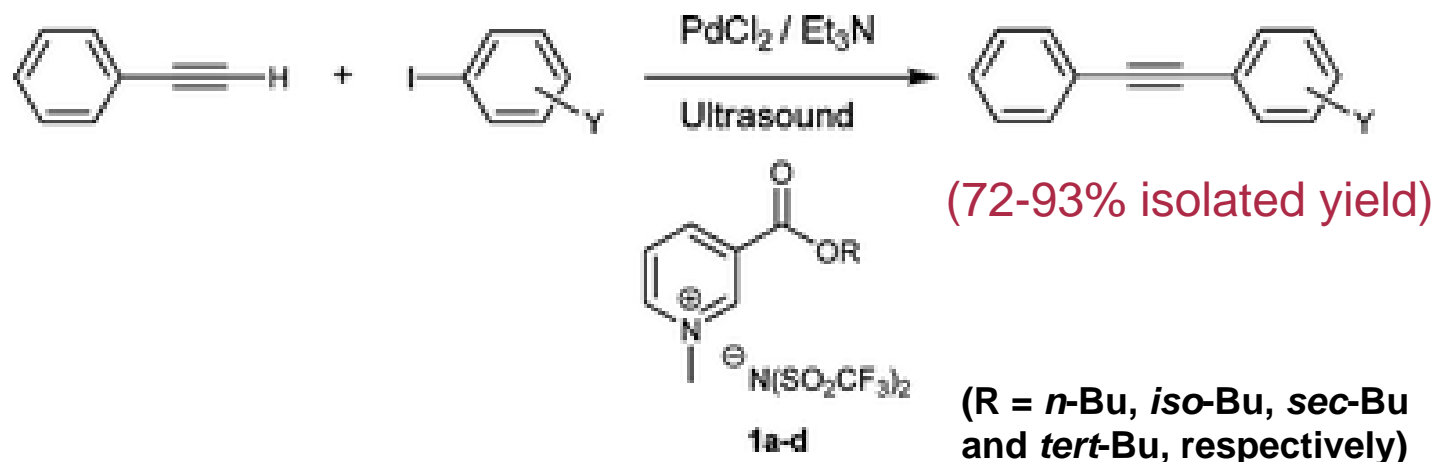
(*Green Chem.* **2009**, *11*, 1428-1432)



Sonogashira coupling in biodegradable ionic liquids derived from nicotinic acid

Harjani, et al., *Green Chem.*, **2010**, *12*, 650 – 655

The biodegradable (68-72% in 28 days) ionic liquids, 3-butoxycarbonyl-1-methylpyridinium bis(trifluoromethanesulfonyl)imides (**1a-d**), have been evaluated as solvents for copper- and phosphine-free Sonogashira coupling reactions. The stability of these ionic liquids toward basic conditions was analysed.



Biodegradation studies of ionic liquids

Coleman and Gathergood, *Chem. Soc. Rev.*, **2010**, *39*, 600 - 637



Large scale preparations using IL

Company	Process	IL is acting as:	Scale
BASF	acid scavenging	auxiliary	commercial
	extractive distillation	extractant	pilot
	chlorination	solvent	commercial
IFP	olefin dimerization	solvent	pilot
Degussa	hydrosilylation	solvent	pilot
	compatibilizer	performance additive	commercial
Arkema	fluorination	solvent	pilot
Chevron Phillips	olefin oligomerization	catalyst	pilot
Scionix	electroplating (Cr)	electrolyte	pilot
Eli Lilly	cleavage of ether	catalyst/reagent	pilot
Air Products	storage of gases	liquid support	pilot
Iolitec/Wandres	cleaning fluid	performance additive	commercial
Linde	gas compression	liquid piston	pilot

Ionic Liquids in Synthesis (Vol. 2), p. 665

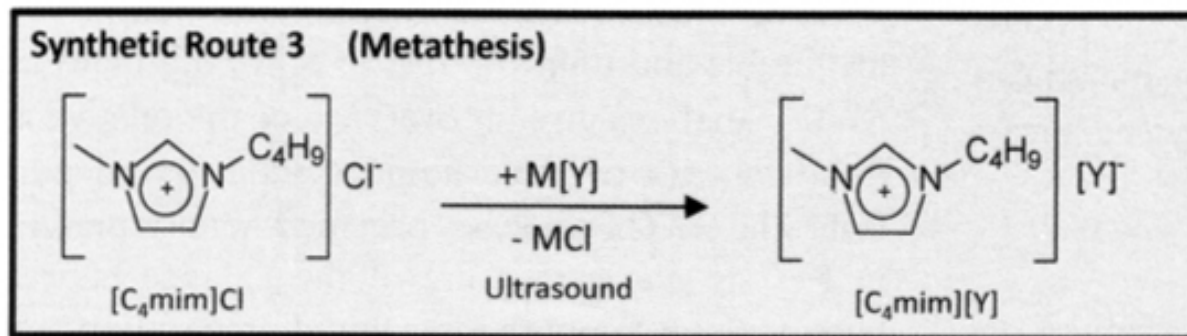
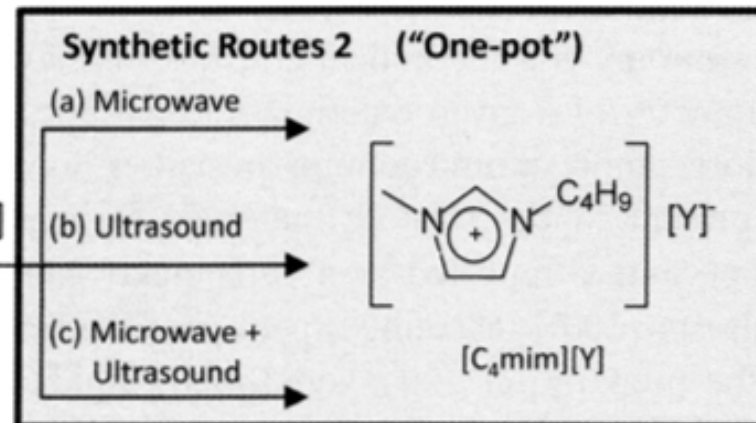
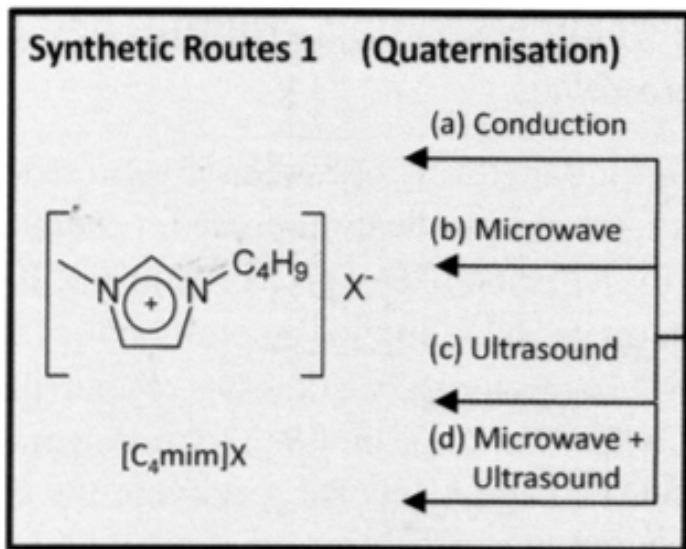


Assessing the greenness of some typical laboratory ionic liquid preparations

Dectlefs and Seddon, *Green Chem.* 2010, 12, 1-17

SWOT analyses (current **s**trengths, current **w**eaknesses, potential future strengths-**o**pportunities, and potential future weakness-**t**hreats) based on 12 principles (only 8 are applied), %atom economy and E-factor.

A series of 1-alkyl-3-methylimidazolium salts were studied via eight routes. Route 1b (microwave) seems to be the best, “but not green enough.”



M = Li, Na or K
Y = CF₃SO₃ or N(SO₂CF₃)₂



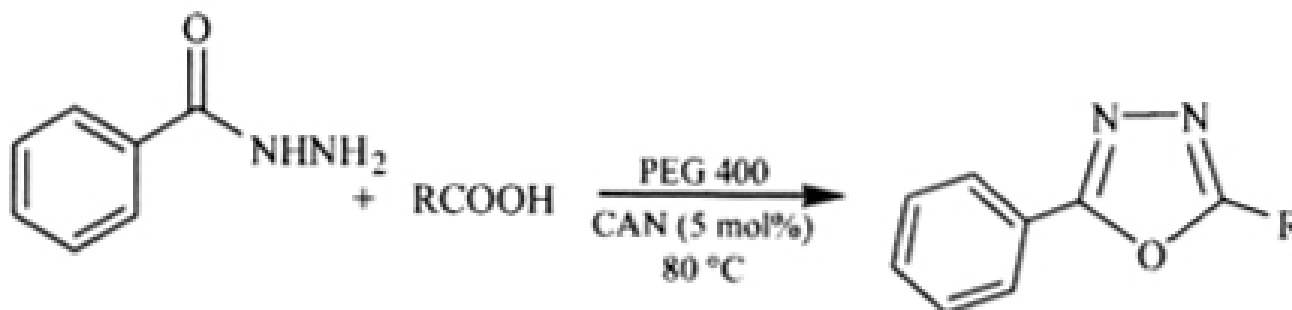
<p>S</p> <ul style="list-style-type: none">i. Rapidii. Energy efficientiii. Flexible reaction scalesiv. Solvent-free synthesisv. High atom economyvi. Excellent E-factor	<p>W</p> <ul style="list-style-type: none">i. Lack of energy efficiency dataii. Expensive apparatusiii. Ionic liquid discolourationiv. Ionic liquid decompositionv. Mass transfer issuesvi. Scale-up very expensive
<p>O</p> <ul style="list-style-type: none">i. Green process developmentii. Quantitative energy input dataiii. Reactor designiv. Intellectual property	<p>T</p> <ul style="list-style-type: none">i. Expensive operationii. <i>In-situ</i> reaction monitoringiii. Safety controls

Fig. 8 SWOT analysis for the preparation of ionic liquids using microwave irradiation.



Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles catalyzed by CAN in PEG

(Kidwai, et al., *Green Chem. Lett. Rev.* **2010**, 3, 55-59)



PEG was found the better solvent (faster and higher yield) than acetonitrile, ethanol and toluene. With 5 mole% of catalyst the reaction was done in 5 hr. The mixture was cooled in dry ice-acetone bath to precipitate PEG, and extracted with ether (PEG being insoluble). Isolation yield was 97-98%. The PEG (2% loss) could be reused for at least three times.



敬請不吝指教

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